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Expedient synthesis of 4-*O*-methylhonokiol via Suzuki–Miyaura cross-coupling

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ABSTRACT

Concise and practical synthesis of 4-*O*-methylhonokiol was achieved in 34% overall yield. The key features of our synthesis include chemoselective *ortho*-mono bromination of phenol as well as biaryl formation via Suzuki–Miyaura cross-coupling, in which bromophenol was reacted with potassium aryltrifluoroborate using $Pd(OAc)_2$ and RuPhos under microwave conditions.

1. Introduction

4-*O*-Methylhonokiol (**1**) was isolated from *Magnolia* species[1] and found to exhibit various biological activities.[2] The bark of the root and stem of *Magnolia* species has long been used as a traditional medicine to treat various disorders and the main bioactive compounds isolated from M. families are biphenyl-neolignans, such as honokiol (**2**), magnolol (**3**), and obovatol (**4**) as shown in Fig. 1.[2] Interestingly, 4-*O*-methylhonokiol (**1**) has the higher anti-inflammatory activity (e.g., IC_{50} of 0.06 μM for COX-2) than honokiol (**2**) and a variety of honokiol analogs.[3] Moreover, 4-*O*-methylhonokiol (**1**) was recently found to exhibit neurotropic and memory improving activity.[2] The structural feature of 4-*O*-methylhonokiol (**1**) is the unsymmetrical 5,3′-diallyl-biphenyl, which differs from honokiol (**2**) by the methoxy group at C4 of the B ring (Fig. 1).

In spite of its interesting biological activities, only pioneering total synthesis of 4-*O*-methylhonokiol (**1**) has been reported by Denton group.[4] On the other hand, the synthesis of the congener, honokiol, has been reported by four groups.[5] However, to the best of our knowledge, regioselective *O*-methylation at the honokiol's B ring is very difficult to achieve for establishing a viable access to 4-*O*-methylhonokiol (**1**). For future profiling and development of 4-*O*-methylhonokiol (**1**) and its analogs, we needed to plan ahead and develop a scalable synthesis suitable for quickly securing multigram quantities. Herein, we describe a short and efficient synthesis of 4-*O*-methylhonokiol (**1**) featuring a Suzuki–Miyaura cross-coupling as the key step.

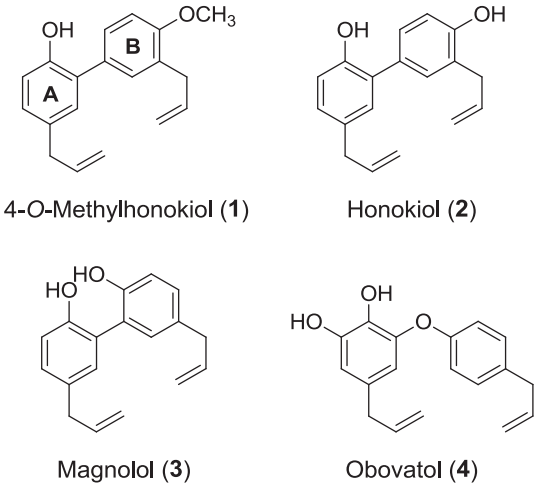

Fig. 1. Representative neolignans isolated from the *Magnolia* species.

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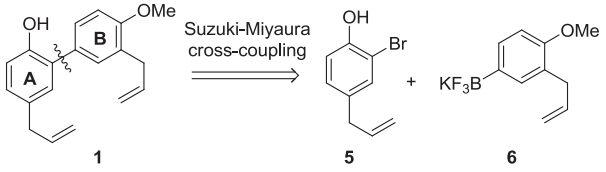
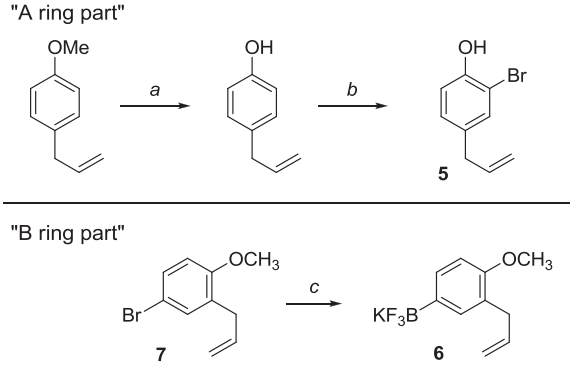
2. Results and discussion

Our plan for the preparation of 4-*O*-methylhonokiol (**1**) entailed linking of 4-allylphenol part (A ring) with 2-allylanisole part (B ring) via a Suzuki–Miyaura cross-coupling.[6] This strategy would permit significant flexibility in synthesis of **1** and thereby adapt a platform that leads to a variety of derivatives for further structure–activity relationship studies. In addition, since the potassium aryltrifluoroborate salts (RBF_3K) have emerged as very important organometallic reagents for Suzuki–Miyaura cross-coupling due to their stability in air and moisture,[6a–c] we envisioned our synthesis would become very useful for a future large-scale synthesis by establishing the key Suzuki–Miyaura cross-coupling utilizing a potassium aryltrifluoroborate. The previous reports[5c,d] for honokiol synthesis involved a methyl ether protection on the A-ring's phenol moiety for the Suzuki–Miyaura coupling. We predicted that the selective mono-deprotection after coupling the two aryl units would be extremely challenging for 4-*O*-methylhonokiol (**1**) synthesis. With all these perspectives, we were thus prompted at designing our synthesis by exploring the Suzuki–Miyaura coupling of the un-protected bromophenol (**5**) and the potassium aryltrifluoroborate (**6**) (Scheme 1).



Scheme 1. Retrosynthetic analysis of 4-*O*-methylhonokiol (**1**).

We set out the synthesis of **1** by the practical preparation of two segments; 2-bromide-4-allylphenol (**5**) and potassium 3-allyl-4-methoxyphenyl-trifluoroborate (**6**), respectively (Scheme 2). We previously reported the synthesis of obovatol (**4**) via chemoselective *ortho*-bromination of phenol and Cu-catalyzed diaryl ether synthesis.[7] Thus, aryl bromide **5** was prepared using our modified bromination conditions from 4-allylphenol, which was obtained via the demethylation of the commercially available 4-allylanisole (MeMgI, 180 °C). 4-Allylphenol was treated with *i*-PrMgCl (1 equiv) as a base and DBDMH (1,3-dibromo-5,5-dimethylhydantoin, 0.5 equiv) to afford the resulting monobromide **5** in good yield (54%, 85% brsm). It is noteworthy that this mono bromination is preferable to the previous procedures in terms of chemical yield and the number of steps and amenable to large-scale preparation of product.[8] On the other hand, aryltrifluoroborate **6** was obtained as a crystalline solid through the treatment of the known 2-allyl-4-bromoanisole **7**[9,10] with *n*-BuLi and B(O*i*-Pr)$_3$, followed by the addition of inexpensive KHF_2.[11] It's worth to note that the two sequences could be run on large scale.



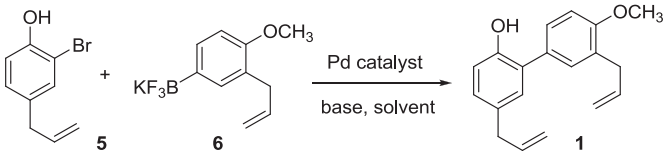
Scheme 2. Reagents and conditions: (a) MeMgI, 180 °C, 81%. (b) *i*-PrMgCl, DBDMH, Et_2O, −78 °C to rt, 24 h, 54% (brsm 85%) (c) *n*-BuLi, B(O*i*-Pr)$_3$, THF, 1 h, then 1 *N* KHF_2 (aq), 30 min, 61%.

With multi-gram quantities of bromophenol **5** and aryltrifluoroborate **6** in hand, we addressed the key Suzuki–Miyaura cross-coupling. To this end, we screened a variety of conditions varying palladium catalysts, ligands and solvents.[6] Representative results are illustrated in Table 1. In initial studies, it was revealed that typical coupling conditions were not eligible to afford the desired biaryl adduct (Table 1, entry 1–8), implying that the coupling is potentially challenged by the un-protected phenol of **5**,[12] although the treatment of $PdCl_2(dppf)\cdot CH_2Cl_2$ and Cs_2CO_3 in MeOH gave the desired product in 12% yield (entry 5). We also conducted the microwave reaction using $PdCl_2(dppf)\cdot CH_2Cl_2$ and K_2CO_3, but the desired product was not obtained (entry 7). Next, we exploited the Molander's modified condition utilizing $Pd(OAc)_2$, K_2CO_3, and Buchwald's phosphine (RuPhos and XPhos). To our delight, the coupling reaction using RuPhos as the phosphine ligand and a solvent mixture of DME and water at 130 °C (microwave, 10 min) afforded the desired product in 72% yield (entry 11). In case of XPhos ligand, the relatively moderate yield arose in the mixture of toluene and water, similar with using RuPhos (entries 9 and 12). It should be noted that the optimized condition could be useful for the synthesis of various analogs of 4-*O*-methylhonokiol.

3. Conclusion

In summary, the total synthesis of 4-*O*-methylhonokiol (**1**) has been completed in 34% overall yield from the 4-bromophenol. Prominent features include the chemoselective *ortho*-mono bromination of 4-allylphenol and the Suzuki–Miyaura biaryl formation with the potassium aryltrifluoroborate and the un-protected bromophenol. Further efforts are in progress for the synthesis of 4-*O*-methylhonokiol derivatives in light of the structure–activity relationship for anti-inflammatory and neurotropic effects.

Table 1
Suzuki–Miyaura cross-coupling of 2-bromo-4-allylphenol **5** and potassium aryltrifluoroborate **6**[a]



Entry	Pd catalyst and ligand	Base	Solvent	Temp (°C)	Time (h)	Yield (%)
1	$Pd(PPh_3)_4$	K_2CO_3	MeOH	80	2	NR[b]
2	$Pd(PPh_3)_4$	K_2CO_3	Toluene/H_2O	80	2	Trace
3	$Pd_2(dba)_3$	K_2CO_3	Toluene/H_2O	80	2	NR
4	$Pd(OAc)_2$	K_2CO_3	Toluene/H_2O	80	2	Trace
5	$PdCl_2(dppf)CH_2Cl_2$	Cs_2CO_3	MeOH	80	2	12
6	$PdCl_2(dppf)\cdot CH_2Cl_2$	Cs_2CO_3	Toluene/H_2O	80	2	NR
7	$PdCl_2(dppf)\cdot CH_2Cl_2$	K_2CO_3	Toluene/H_2O	70[c]	20 min	NR
8	$PdCl_2(TPP)$	K_2CO_3	Toluene/H_2O	80	2	Trace
9	$Pd(OAc)_2$/RuPhos	K_2CO_3	Toluene/H_2O	80	2	27
10	$Pd(OAc)_2$/RuPhos	K_2CO_3	DME/H_2O	80	1	66
11[c]	*$Pd(OAc)_2$/RuPhos*	*K_2CO_3*	*DME/H_2O*	*130*	*10 min*	*72*
12	$Pd(OAc)_2$/XPhos	K_2CO_3	Toluene/H_2O	80	2	32
13	$Pd(OAc)_2$/XPhos	K_2CO_3	DME/H_2O	80	4	Trace

[a] Reaction condition: Conducted with Pd (10 mol %), ligand (20 mol %), base (3 equiv), **5** (1 equiv), and **6** (1 equiv).
[b] No reaction.
[c] Microwave-assisted reaction (irradiation power 100 W).

4. Experimental section

4.1. General information

Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Air and moisture sensitive reactions were performed under an argon atmosphere. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck). Melting points were measured on an Electrothermal IA 9100 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Jasco FT-IR 4100 spectrometer. Low and high-resolution fast atom bombardment (FAB) mass spectra were obtained with JEOL JMS-700 instrument. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker AVANCE III 400 MHz or Bruker AVANCE 500 MHz Spectrometer as solutions in deuteriochloroform ($CDCl_3$) or deuterioacetone (CD_3COCD_3). ^{1}H NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet and/or multiple resonances), number of protons, and coupling constant in hertz (Hz).

4.2. Experimental procedure

*4.2.1. 2-Allyl-4-bromo-1-methoxybenzene (**7**).* A mixture of anhydrous K_2CO_3 (4.2 g, 30 mmol), 2-allyl-4-bromophenol (3.2 g, 15 mmol), and acetone (30 mL) was stirred for 30 min then iodomethane (2.7 g, 19 mmol) was added at room temperature. After 4 h, solvent was evaporated then water (15 mL) was added. The mixture was extracted with ether (3×20 mL). The combined extracts were washed with water (10 mL), dried over anhydrous $MgSO_4$ and the solvent was evaporated. Purification on silica gel (hexane only) provided 2-allyl-4-bromo-1-methoxybenzene (**7**) (3.7 g, 94%) as a pale yellow oil; IR (thin film) 3081,1638, 1488, 1242, 1032, 803, 654 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (dd, 1H, J=8.6, 2.5 Hz), 7.24 (ds, 1H, J=2.5 Hz), 6.72 (d, 1H, J=8.6 Hz), 5.94 (m, 1H), 5.06 (m, 2H), 3.80 (s, 3H), 3.34 (d, 2H, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ. 156.4, 136.0, 132.4, 131.0, 129.8, 116.1, 112.7, 112.0, 55.6, 33.9.

*4.2.2. Potassium 3-allyl-4-methoxyphenyltrifluoroborate (**6**).* To a mixture of **7** (0.72 g, 3.2 mmol) and triisopropyl borate (0.60 g, 3.2 mmol) in THF (30 mL) was slowly added *n*-BuLi (1.6 M soln in hexane, 2.0 mL, 3.2 mmol) at −78 °C for 20 min. The reaction mixture was vigorously stirred for 1 h at −78 °C and then warmed to rt for 40 min. After the reaction was completed, 1 N KHF_2 (9.0 mL, 9.0 mmol) was added at rt. After stirring for 30 min, the suspension was concentrated and dried in vacuo for 3 h. The residual white solid was dissolved in dry acetone (15 mL), and the insoluble salts were filtered off through Celite. The solvent was concentrated on a rotary evaporator, and then redissolved in a minimal amount of acetone. The addition of ether led to the precipitation of the product. The product was filtered, collected, and dried in vacuo to afford the desired potassium 3-allyl-4-methoxyphenyltrifluoroborate (**6**) (0.50 g, 61%) as a white solid; mp 75–78 °C; IR (thin film) 1637, 1241, 1133, 1009, 911, 736 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.29 (d, 1H, J=7.9 Hz), 7.27 (s, 1H), 6.70 (d, 1H, J=7.9 Hz), 5.98 (m, 1H), 5.00 (m, 1H), 4.91 (m, 1H), 3.75 (s, 3H), 3.31 (d, 2H, J=6.6 Hz); ^{13}C NMR (100 MHz, aceton-d_6) δ 155.4, 138.4, 133.4, 130.6, 125.3, 113.4, 108.8, 54.6, 34.6; HRMS (FAB) calcd for $C_{10}H_{11}BF_3OK$ (M^+): 254.0492; found 254.0482.

*4.2.3. 4-O-Methylhonokiol (**1**).* To a glass vessel containing a stirring bar was added potassium 3-allyl-4-methoxyphenyl-trifluoroborate (**6**) (254 mg, 1.00 mmol), 4-allyl-2-bromophenol **5** (213 mg, 1.00 mmol), $Pd(OAc)_2$ (22.5 mg, 0.100 mmol, 10 mol %), RuPhos (2-dicyclohexylphosphino-2′,6′-diisopropoxy-biphenyl, 94.0 mg, 0.20 mmol, 20 mol %), and K_2CO_3 (420 mg, 3.00 mmol). The vessel was sealed with a septum, and DME/H_2O (v/v=5:1, 20 mL) was added via syringe. The reaction was heated by microwave (Biotage® Initiator, EXP EU 355301, 115 W) at 130 °C for 10 min. After the aryl bromide was totally consumed (the reaction was monitored by TLC), the reaction mixture was cooled to rt. The residual compound was dissolved in ethyl acetate (100 mL), and the insoluble salts were filtered through a thin pad of silica gel. The combined organic layers were washed with H_2O, and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification via flash column chromatography (EtOAc/hexanes=1:10) of the residue afforded 202 mg (72%) of **1** as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J=8.4 Hz, 1H), 7.25 (m, 1H), 7.05 (m, 2H), 6.97 (d, J=8.4 Hz, 1H), 6.92 (d, J=8.4 Hz, 1H), 6.08–5.93 (m, 2H), 5.13–5.05 (m, 5H), 3.89 (s, 3H), 3.44 (d, J=6.8 Hz, 2H), 3.36 (d, J=6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 151.0, 138.0, 136.7, 132.4, 130.7, 130.4, 130.0, 129.2, 129.0, 128.1, 128.0, 116.1, 115.8, 115.7, 111.1, 55.7, 39.6, 34.5; LRMS (FAB) m/z 281 ($M+H^+$).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.09.115. These data include MOL files and InChiKeys of the most important compounds described in this article.

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