Total Synthesis of Honokiol by Selective Samarium-Mediated Allylic Benzoate Reduction

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Abstract. The total synthesis of the biologically relevant compound honokiol has been completed featuring a samarium-mediated bis-benzoyl ester reduction to simultaneously install both allyl substituents found in the natural product. This reaction was performed after a Suzuki coupling was used to generate the biphenyl core, thereby avoiding problems associated with the acidity of these allyl groups and their propensity to isomerize. In this way, the synthesis of honokiol could be completed in 4 steps and 42% overall yield.

Honokiol (**1**) is a neolignan contained in the bark of *Magnolia occifinalis* that continues to elicit significant interest due to its range of promising biological activities including both antitumor¹ and anti-angiogenic² properties (Figure 1). Isolation of honokiol from the natural source is hampered by the presence of its isomeric compound magnolol (**2**).³ The different bioactivities of magnolol⁴ yet very similar physical properties to honokiol makes separation both necessary and challenging.⁵ Thus several groups have pursued a total synthesis of honokiol,⁶ the first by Takeya et al.^{6a} in 1986 and more recently Harada et al. in 2014.^{6h} Many of these syntheses have utilized an aromatic Claisen rearrangement (Figure 2).^{6a,c-f} This reaction is however limited in terms of regiochemistry, used primarily to generate ortho-allyl substituted phenols.⁷ For instance Reddy et al. reported obtaining roughly 1:1 mixtures of honokiol (**1**) and isohonokiol (**3**) from the bis-*O*-allylbiphenyl **4**.^{6f}

Figure 1. Natural products honokiol (**1**) and magnolol (**2**) and previous Claisen rearrangement-based synthesis.

Recently, our group reported a general approach to non-conjugated olefins of this type by samarium-mediated benzoyl ester elimination/isomerization.⁸ The reaction is proposed to occur via an organosamarium intermediate of type **5**, accessible via allylic benzoates **6** or **7** (Scheme 1). Internal delivery of a proton from a coordinated proton donor (e.g. water) then leads selectively to non-conjugated products as the major isomer. We then demonstrated that this

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reaction could be used to synthesize two properly functionalized allyl-substituted benzenes **8** and **9** en route to a synthesis of honokiol. Herein we report a completion of the synthesis of honokiol, ultimately using our samarium chemistry to incorporate both allyl groups simultaneously. The synthesis could be accomplished in 4 steps and 42% overall yield.

Scheme 1. Synthesis of allylbenzenes by samarium-mediated benzoyl ester elimination/isomerization and application to honokiol from products **8** and **9**.

Previously, we had reported that commercial aldehydes **10** and **11** could be converted to **8** and **9** via allylic benzoates **12** and **13** by samarium-mediated benzoyl ester reduction (Scheme 2).⁸ With water as the proton source, **8** and **9** were obtained in 60% and 76% yield respectively, with only marginal selectivity for the non-conjugated (γ) vs. the conjugated (α) isomer (γ : α = 85:15 for **8** and 65:35 for **9**, Scheme 2). After some experimentation it was found that by switching to methanol as the additive,⁹ both the yields and selectivities for these reactions greatly improved, affording **8** and **9** in $\geq 90\%$ yield and $>10:1$ selectivity for the γ -isomer. Hasegawa has reported that samarium diiodide is less stable with water than methanol in tetrahydrofuran,¹⁰ generating Lewis acidic $\text{Sm}(\text{III})$ that may explain in part the improvements afforded by methanol. Efforts are ongoing to better understand the effects of additives and proton sources in these reactions.

Scheme 2. Optimized synthesis of honokiol fragments **8** and **9** by samarium benzoyl ester reduction.

With improved access to compounds **8** and **9**, we then began our investigations into their coupling to form the biphenyl core of honokiol. Initial experiments involved conversion of **8** or **9** into their corresponding organometallic compounds (Mg , Zn , Li) and subsequent palladium catalyzed cross-coupling (Scheme 3).^{11,12} Unfortunately none of these reactions produced appreciable amounts of the desired cross-coupled product **14** as detectable by NMR or GC-MS.

We surmised that the failure of these reactions could be blamed on the acidic benzylic/allylic protons ($pK_a \sim 33$)¹³ that were interfering with the metal-halogen exchange. This was further supported by a deuterium labeling experiment performed on compound **9**. Treatment of **9** with ^tBuLi (2.2 equiv) and quenching with D₂O afforded a mixture of compounds with labeling observed at the benzylic position by ¹H NMR.

Scheme 3. Attempted cross-coupling of compounds **8** and **9**.

We therefore turned our attention to a Suzuki coupling since the requisite boronate esters could be prepared and isolated under more mild palladium catalysis.¹⁴ However under the conditions tried,¹⁵ we found that conversion of **8** and **9** to their corresponding boronate esters was accompanied by some alkene isomerization (Scheme 4). The sensitivity of these allyl groups toward isomerization had also been described by both Chen^{6c} and Denton^{6d} in their syntheses of honokiol, requiring the somewhat specialized *S*-Phos ligand for their cross-couplings.

Scheme 4. Allylic isomerization during conversion of **8** and **9** to their corresponding boronate esters.

In an attempt to avoid the problems encountered with the allyls, a new synthesis was devised whereby these groups would be installed at a later stage. More specifically, we envisioned inverting the samarium and palladium steps, forming the biphenyl core first followed by benzoyl ester synthesis and bis-samarium reduction. To that end, we began by investigating the Suzuki cross-coupling of aldehydes **10** and **11**. Boronate ester formation from **11** proved higher yielding than from **10** under the same conditions,¹⁵ presumably as a result of increased sterics from the neighboring methoxy group (Scheme 5). We therefore focused on finding suitable conditions for the coupling of bromide **10** with boronate ester **15**. Ultimately the use of bis(tri-*tert*-butylphosphine)palladium as catalyst and aq. Na_2CO_3 as base in dioxane at 70 °C proved optimal, giving the dialdehyde **16** in excellent yield. This cross-coupling could be performed with or without isolation of the boronate ester **15** (i.e. adding **10** and $Pd(tBu_3P)_2$ directly to the flask in which **15** was formed) and on multi-gram scale in consistently high yields.

Scheme 5. Suzuki coupling-based synthesis of dialdehyde **16**.

Conversion of **16** to the bis-benzoyl ester could be performed in a single step by vinyl Grignard addition and trapping with benzoyl chloride (Scheme 6), although we generally opted to isolate the intermediate diol **17** for easier purification. Acylation of **17** with benzoyl chloride followed by treatment with SmI_2/MeOH resulted in very clean reduction of both benzoyl esters, giving dimethylhonokiol (**18**) in 98% yield and >10:1 selectivity for both non-conjugated allyl by ^1H NMR analysis. It is worth noting the ability of this samarium procedure to generate sensitive olefins that are prone to isomerization under conditions like palladium catalysis,^{6c,d} as yet another example of the utility of samarium diiodide for organic synthesis.¹⁶ At this point we had bisected the synthesis of Srinivas,^{6g} however as opposed to AlCl_3/DMS they reported for the demethylation of **18**, our best yields were obtained using the tris(pentafluorophenyl)borane/ Et_3SiH system introduced by Gevorgyan et al.¹⁷ In this way, the synthesis of honokiol was completed in 42% overall yield from commercial aldehydes **10** and **11**.

Scheme 6. Completion of the synthesis of honokiol.

In sum, a novel total synthesis of the medicinally important compound honokiol has been completed featuring a samarium-mediated bis-benzoyl ester reduction to simultaneously install both allyl substituents found in the natural product. By incorporating these groups at a later stage, we were able to avoid problems associated with allylic deprotonation or isomerization observed under palladium catalyzed cross-coupling conditions. It is anticipated that this sequence may be scaled up to make larger quantities of honokiol available for further biological testing

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