Total Synthesis of Gibbilimbols A−D

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Gibbilimbols A−D (**1**−**4**) were synthesized in 32−49% yield over four steps from commercially available starting materials. A copper-catalyzed coupling of 4-methoxyphenylmagnesium bromide with various unsaturated alkyl bromides was the key step in assembling the (long-chain alkyl)-phenol skeleton.

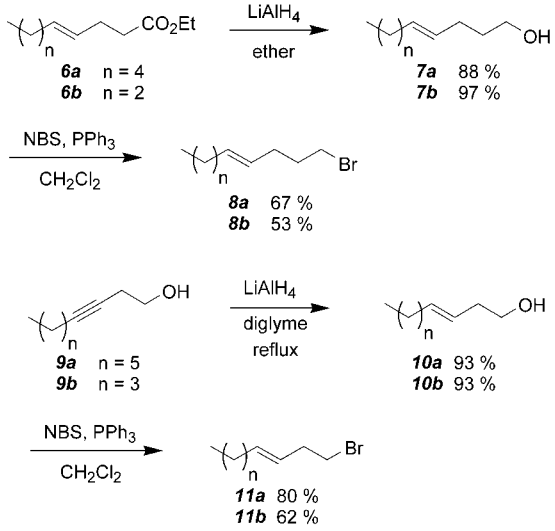
Introduction

Nonisoprenoid phenolic lipids exist in a wide variety of plant species and in a few bacteria. These compounds are derived from the shikimate and polyketide pathways and include alkylmonophenols, -catechols, -resorcinols, and -hydroquinones.[1] Several (long-chain alkyl)phenols, especially the 5-alkylresorcinols and anacardic acids, have attracted attention due to their biological activities.[2]

Gibbilimbols A−D (**1**−**4**) are 4-alkenylphenols recently isolated in small quantities from the leaves of *Piper gibbilimbum* (Figure 1).[3] The gibbilimbols have an (*E*)-alkene in the 3′ or 4′ position of their 8- or 10-carbon side chains and were found to exhibit modest cytotoxicity toward KB nasopharyngal cancer cells (ED_{50} 2−8 μg/mL) and antibacterial activity against *Staphylococcus epidermidis* and *Bacillus cereus* (MIC 2−4 μg/mL).[3] A similar alkenylphenol (**5**) with an (*E*)-alkene in the 5′ position of a 16-carbon side chain has been isolated from *Piper hispidum*.[4] In the case of **5** determining the position of the alkene in the side chain was not trivial, and the 5′ position was deduced from double-resonance ^{1}H NMR experiments.[4]

The genus *Piper* consists of more than 1400 species and includes shrubs, high-climbing woody vines, and small trees which exist mostly in tropical regions.[5,6] The most well-known member of this family, *Piper nigrum*, has been prized in the spice trade for centuries for the black pepper it produces. Most *Piper* species have also found broad application in traditional medicine.[6] The leaves of *P. gibbilimbum*, a small shrub that grows in the Central Province of Papua, New Guinea, are used there to treat fever, abscesses, and ulceration of the skin, and the juice squeezed from the heated bark is taken for suspected cancer or internal sores.[7,8]

Scheme 1



We were prompted to undertake the synthesis of the gibbilimbols due to their biological activity and relative scarcity (2−12 mg each of **1**−**4** from 1.2 kg of dried *P. gibbilimbum* leaves). In designing a synthesis of these compounds, we wished to minimize not only the number of linear steps from commercially available materials, but also the number of different transformations required. Thus, we settled on a strategy that attaches each side chain to the aromatic core via a copper-catalyzed Grignard alkylation. We now report the total synthesis of gibbilimbols A−D (**1**−**4**).[9,10]

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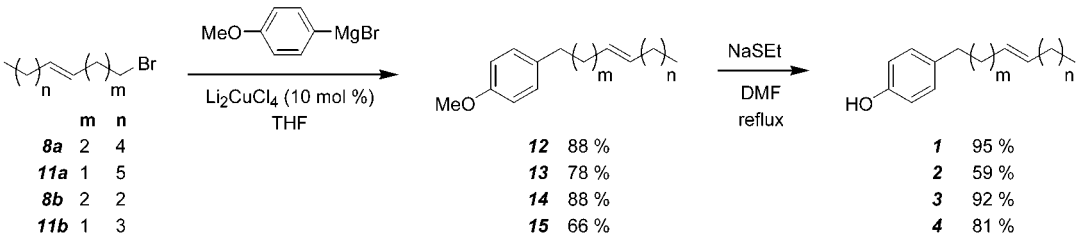
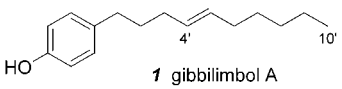
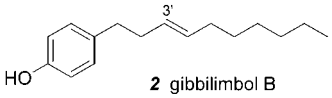
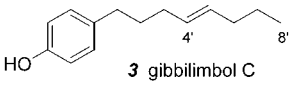
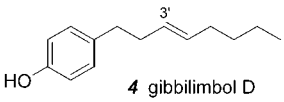
Scheme 2











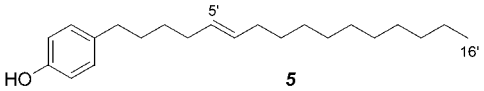


Figure 1. Alkenylphenols isolated from *Piper* species.

Results and Discussion

The side chains for the gibbilimbols were prepared in a straightforward manner from inexpensive starting materials (Scheme 1). Commercially available esters **6a** and **6b** were reduced to the corresponding alcohols **7a** and **7b** with lithium aluminum hydride in excellent yield. The alcohols were then converted to bromides **8a** and **8b** using *N*-bromosuccinimide and triphenylphosphine[11] in moderate to good yields after purification by vacuum distillation to remove small amounts of higher boiling dibrominated material arising from allylic bromination.

Dissolving metal reduction of commercially available alkynols **9a** and **9b** did not go to completion in our hands,[12] but reduction of the alkyne with lithium aluminum hydride in refluxing diglyme[13] provided the (*E*)-alkenols **10a** and **10b** in excellent yield (Scheme 1). Treatment of the alcohols **10** with *N*-bromosuccinimide and triphenylphosphine provided bromides **11a** and **11b** after vacuum distillation as described above.

The alkyl bromides **8** and **11** underwent reaction with 4-methoxyphenylmagnesium bromide in the presence of lithium tetrachlorocuprate[14] to provide the cross-coupled products **12**−**15** in good to excellent yields (Scheme 2). The Grignard reagent was prepared in the usual fashion by reacting 4-bromoanisole with magnesium turnings in refluxing tetrahydrofuran. This process was monitored by gas chromatography, which showed the disappearance of 4-bromoanisole and the appearance of anisole (formed by protonation of 4-methoxyphenylmagnesium bromide during the aqueous quench) as the sole product. The homocoupling product 4,4′-dimethoxybiphenyl was not detected by GC during formation of the Grignard reagent, but a significant amount of this side product was detected after the addition of the alkyl bromide **8** (and **11**) and the lithium tetrachlorocuprate catalyst. It is likely that the 4,4′-dimethoxybiphenyl is formed from in situ reduction of the Cu(II) species to the active copper(I) catalyst.[15] Thus, reactions were conducted with a slight excess of 4-methoxyphenylmagnesium bromide. Separation of 4,4′-dimethoxybiphenyl from cross-coupling products **12**−**15** was more difficult than anticipated due to the compounds having similar mobilities on silica. The majority of the homocoupling impurity could be removed by dissolving the crude product mixture in a minimum amount of boiling hexanes, allowing the solution to cool, and removing the resulting solid 4,4′-dimethoxybiphenyl by filtration. The filtrate was then concentrated and subjected to final purification by flash chromatography.

The last step in the synthesis of the gibbilimbols was deprotection of the phenol group. Treatment of **12** with boron tribromide resulted not only in the cleavage of the methyl ether, but also in reaction of the alkene.[16] The ^{1}H NMR spectrum of the crude product revealed nearly complete loss of the vinyl proton resonances. Analysis of the complex mixture by GC/MS revealed products formed from HBr addition to the alkene as well as products likely formed by cyclization processes. Treatment of **12** with excess sodium ethanethiolate in refluxing *N*,*N*-dimethylformamide[17] produced gibbilimbol A (**1**) in excellent yield, however (Scheme 2). Similar reaction of methyl ethers **13**−**15** yielded gibbilimbols B−D (**2**−**4**), respectively, in good to excellent yield. The IR, ^{1}H NMR, ^{13}C NMR, and LRMS data for synthetic gibbilimbols A−D (**1**−**4**) match those reported for the natural products.[3]

Conclusions

Gibbilimbols A−D were each synthesized in just four steps from commercially available starting materials in 32−49% overall yield. The copper-catalyzed coupling of

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4-methoxyphenylmagnesium bromide with alkyl bromides **8** and **11** is an efficient and readily scalable approach to a variety of biologically active (long-chain alkyl)phenols and -resorcinols.

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Supporting Information Available: Experimental details and characterization data for all synthesized compounds and ^{1}H and ^{13}C NMR spectra of compounds **1**−**4**, **8**, and **11**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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