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Concise access to primin, miconidin and related natural resorcinols

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ABSTRACT

An efficient and short synthetic procedures affording the biologically active natural products primin, miconidin, olivetol, grevillol, and cardol (adipostatin A) in high yields are reported. The two strategies involve Sonogashira and Suzuki cross-couplings as the crucial steps for the installation of the alkyl side-chains. Syntheses start from cheap, commercially available 1-bromo-3,5-dimethoxybenezene to obtain 1,3-dimethoxy-5-(alk-1-yn-1-yl)benzene as the key intermediate. This intermediate can be easily and economically oxidized to provide primin in excellent overall yield while avoiding undesired side products by the virtue of its symmetry. The demethylation of the key intermediate affords natural resorcinols olivetol, grevillol, and cardol, respectively. The reduction of primin provides its hydroquinone derivative miconidin.

1. Introduction

Plants are a vast source of biologically active compounds. However, these compounds are often of complex structure rendering them challenging to synthesize. Even those compounds with simple-looking structures are often scarcely available by common organic chemistry methods. This is also the case for plant quinone primin (**1**) and its reduced form miconidin (**2**) and their related plant resorcinols, olivetol (**3**), grevillol (**4**), and cardol (**5**, adipostatin A, Fig. 1). Despite their structural simplicity and attractive biological activity, they are either not commercially available or their price on the market is as high as $US 100/10 mg.[1] It is caused by their time-consuming and costly isolation from plant material and the lack of appropriately efficient and high-yielding synthesis from accessible compounds.

Primin (**1**), and its reduced form miconidin (**2**), are found in a variety of plants, predominantly in *Primula* genus.[2] Their various biological activities have been studied. For example, primin (**1**) exhibited anti-proliferative activity against M109 murine cancer cells (IC_{50} = 10 μg/mL) and A2780 human ovarian cancer cell line (IC_{50} = 2.9 μg/mL)[3] as well as anti-bacterial activity against *Staphylococcus aureus* (IC_{50} = 8 μg/mL).[4] Even though it also acts as a skin sensitizer causing allergic reaction called primrose dermatitis,[2] it has definitely high potential in medicinal chemistry due to its unique 1,4-benzoquinone structural core able to manipulate redox processes.

In our laboratory, in the search for new anti-inflammatory agents, primin (**1**) and its derivatives were examined for their inhibitory activity against inflammatory enzymes, cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), and 5-lipooxygenase (5-LOX).[5] Primin was comparably active to reference substances in COX-2 and 5-LOX assays thus exhibiting desired dual COX-2/5-LOX inhibitory activity.[5] High 5-LOX inhibitory activity was also reported for miconidin acetate, the hydroquinone derivative of primin.[6] For miconidin itself (**2**), an anti-plasmoidal activity was reported[7] and it was also found to act as insect-detergent.[8]

Natural resorcinols are compounds structurally related to primin. Olivetol (**3**) is found mainly in lichens[9] and some insects.[10] Olivetol (**3**), through its derivative, olivetolic acid, serves as a biosynthetic precursor of cannabinoids, thus can be useful key intermediate in the synthesis of their derivatives. Grevillol (**4**) and cardol (**5**) are plant secondary metabolites exhibiting 5-LOX and COX inhibitory activity,[11] as well as cytotoxic activity against selected human cancer cell lines.[12] Furthermore, these 5-alkylated resorcinols are also structurally similar to another group of biologically active compounds, stilbenoids.

Even though several syntheses of primin have been reported, these suffer from poor yields and/or expensive starting materials. For instance, Watanabe et al.[13] reported primin six-step synthesis

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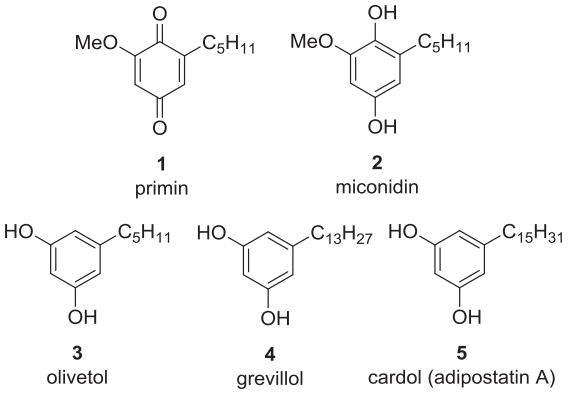


Fig. 1. Structures of primin, miconidin, olivetol, grevillol and cardol. (adipostatin A).

with 56% overall yield starting from 5-iodovanillin and employing Suzuki-Miyaura cross-coupling reaction as the key step. A three-step synthesis starting from *o*-vanillin and using Grignard reaction for the installation of the aliphatic side chain was described by Gunatilaka et al.[3] Despite being short it yielded primin in only 8% overall yield. Grignard reaction was also employed by Bhattacharya et al.[16] in a long, nine-step procedure starting from *o*-vanillin and resulting in 34% overall yield. On the other hand, an interesting four-step strategy starting from guaiacol was designed by Jacob et al.[15] They applied Claisen rearrangement for the crucial alkylation step providing primin in 43% overall yield. All these strategies, however, succumb to an uneconomical final oxidation step due to the utilization of large excess of expensive Fremy's salt or of oxygen/salcomine catalytic system.

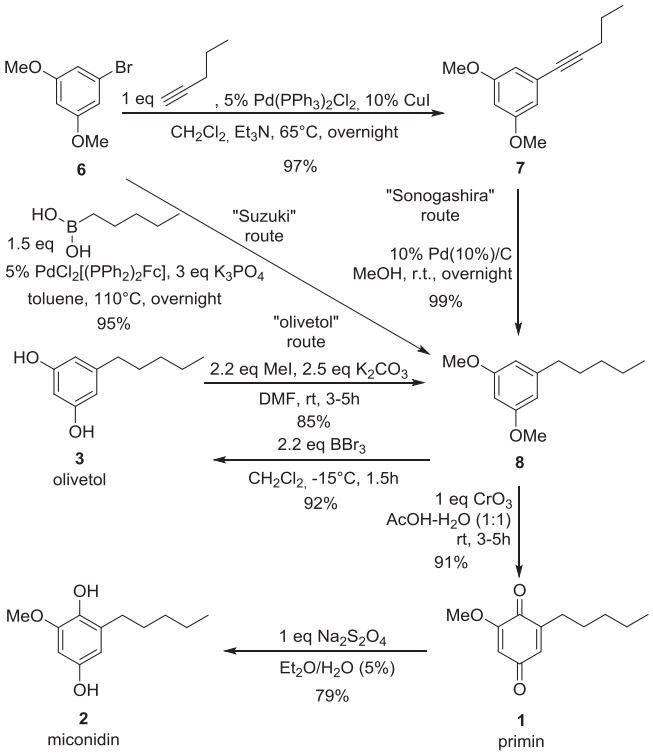
Recently, a one-step synthesis by Nasiri et al.[17] was reported, albeit starting from already expensive 2-methoxybenzo-1,4-quinone. In this strategy, the alkyl chain was introduced by the reaction with analogous alkyl acid or alkyl boronic acid catalyzed by silver nitrate or persulphate. However, this reaction affords maximum 50% yield and, due to poor regioselectivity, a mixture of isomers in ~3:1 ratio with the iso-primin isomer being favored.

In case of 5-alkylated natural resorcinols, various rather long and inefficient syntheses may be found throughout the literature. From these, the methods of Alonso et al.[18] and Wu et al.[19] are the most efficient. Alonso et al.[18] reported five-step synthesis of these resorcinols employing the catalytic reaction of 3,5-dimethoxybenzyl trimethylsilyl ether with suitable aldehyde as the crucial step. In this case, the overall yield was approximately 24%. Shorter and more elegant synthesis was published by Wu et al.[19] who used Wittig reaction as the key reaction in three-step synthesis affording the resorcinols in mediocre 67% overall yield.

2. Results and discussion

Herein, three elegant and high-yielding (77–87%) strategies to provide primin and related compounds are reported, with each preparation offering unique benefits (Scheme 1).

Firstly, the “Sonogashira route” started from cheap, commercially available 1-bromo-3,5-dimethoxybenezene (**6**) and employed Sonogahira cross-coupling for the aromatic alkylation. Various catalysts and conditions were examined in order to obtain the best possible yield. These conditions are summarized in Table 1. Due to the same R_f of the starting material and the product, even when different solvent elution systems were employed, the conversion of the reaction had to be monitored by NMR analysis. Therefore, complete conversion of the starting material is vital to avoid isolation difficulties of the product.



Scheme 1. Syntheses of primin, miconidin and olivetol.

From the optimalization study it was determined that the best conversion was achieved when bis(triphenylphosphine)-palladium(II) chloride was used as a catalyst (entry 1, Table 1). Precise temperature control was found to be essential (compare entry 1 and 2, Table 1). The product, 1,3-dimethoxy-5-(pent-1-yn-1-yl)benzene (**7**) was thus obtained in excellent yield (97%). Subsequent hydrogenation of the triple bond with palladium on carbon at 5 bars hydrogen pressure gave the desired product **8** in almost quantitative yield. The employment of normal atmospheric pressure for the reduction resulted in much longer reaction time (days). The obtained crucial intermediate 1,3-dimethoxy-5-pentylbenzene (**8**) with the requisite regiosymmetry was oxidized using inexpensive chromium(VI) oxide yielding primin (**1**) in 91% yield. This mentioned symmetry forestalls the formation of undesirable mixture of isomers. The immense advantage of this strategy is the excellent overall yield (87%) and the utilization of cheap starting material and reagents.

Secondly, primin may also be obtained via “Suzuki route” using Suzuki cross-coupling for the aromatic alkylation. The synthesis started again from compound **6** enabling incorporation of the pentyl side chain fragment in only one-step. Nevertheless, such

Table 1
Optimization of Sonogoshira cross-coupling to compound **7**.

Entry	Catalyst	Solvent	T(°C)/t(h)	Yield(%)
1	$Pd(PPh_3)Cl_2$	CH_2Cl_2/Et_3N	r.t./16 then 65/2	97
2	$Pd(PPh_3)Cl_2$	CH_2Cl_2/Et_3N	65/16	52[a]
3	$Pd(PhCN)_2Cl_2P(^tBu)_3$	1,4-dioxane/NH^iPr_2	r.t./16	71[a]
4	$Pd(PhCN)_2Cl_2P(^tBu)_3$	DMSO/NH^iPr_2	r.t./16	82[a]
5	$Pd_2(dba)_3$	Et_3N	80/16	10[a]
6	$Pd_2(dba)_3$	Et_3N/toluene	110/40	15[a]
7	$Pd(PPh_3)_4$	Et_3N	80/16	Trace[a]

Conditions: pentyne: 1 (to 1.5 eq), catalyst: 0.05 eq, CuI: 0.1 eq.
[a] Yield determined by ^1H NMR.