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A short synthesis of morachalcone A

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Abstract—Advanced *C*-prenylated intermediates for three aromatase inhibitors, including morachalcone A, can be synthesized through a Claisen–Schmidt condensation followed by Florisil®-catalyzed [1,3]-sigmatropic rearrangement of a prenyl phenyl ether.

The growth of many breast cancers in postmenopausal women is stimulated by estrogen at typical physiological concentrations. One method for the treatment of breast and prostate cancers relies on antiestrogens that bind to an estrogen receptor within the tumor and block the effect of estrogen. Alternatively, tumor growth can be slowed by reducing the circulating concentration of estradiol and estrone by treatment with inhibitors of estrogen biosynthesis.[1] Aromatase, a key cytochrome p450-dependent enzyme, catalyzes aromatization of the androstenedione A ring which is the final and rate-limiting step in the estrone biosynthetic pathway.[2] Therefore, aromatase inhibitors have become attractive breast cancer therapies for women beyond menopause.

Current therapies include the first FDA-approved aromatase inhibitor, aminogluthethimide [3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione (AG)]. AG limits estrogen synthesis by inhibiting adrenal steroid biosynthesis and peripheral aromatase enzyme activity. However, it also inhibits glucocorticoids, leading to an increased secretion of adrenocorticotropic hormone by the pituitary that overpowers the drug's effect in the adrenal gland. A strategy to avoid this deleterious side activity is to identify drugs that will depress peripheral aromatase activity while not affecting the pituitary gland.[3] AG has shown some clinical benefit in breast cancer trials, but lack of selectivity and its weak aromatase inhibitory activity has limited its usefulness.[1] Other aromatase inhibitors recently approved by the FDA include the nonsteroidals anastrazole and letrozole as well as the steroidal exemestane that, like all aromatase inhibitors, inhibit the synthesis of estrogen in tissues other than the ovaries.[4]

There is a continuing search for new therapeutic leads among botanical natural products. Aromatase inhibitors of natural origin have been isolated from organic extracts of the mulberry tree, *Broussonetia papyrifera* (L.) L'Her. Ex Vent (Moraceae),[2] and the osage orange tree, *Machura pomifera*. Fruits of *M. pomifera* have been used for centuries in China to treat impotency and ophthalmic disorders.[5] Several isolates from the mulberry tree have demonstrated antifungal, antioxidant, and lens aldose reductase inhibitory activities.[2]

The current study focuses on the synthesis of one of the aforementioned isolates of the mulberry tree, morachalcone A (**1**). Morachalcone A is an attractive target, exhibiting aromatase inhibitory activity greater than that of the benchmark inhibitor AG ($IC_{50} = 4.9$ vs 6.4 μM for AG).[1,2] Furthermore, morachalcone A has potential synthetic utility as a precursor to isogemichalcone C (**2**) and its desmethoxy analog (**3**). The latter two isolates from the same source demonstrate significant aromatase activity with IC_{50}'s of 7.1 and 0.5 μM, respectively.[2]

Disconnection of the prenyl group of morachalcone A provides a potential precursor (**4**) that leads to all three natural products. We envisioned subsequent disconnection at the bridging olefin, leading to common polyphenolic starting materials (Fig. 1). To initiate the sequence, aldehyde **5** was protected with MOMCl in 82% yield,

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Keywords: [1,3]-Rearrangement; Florisil®; Chalcone.

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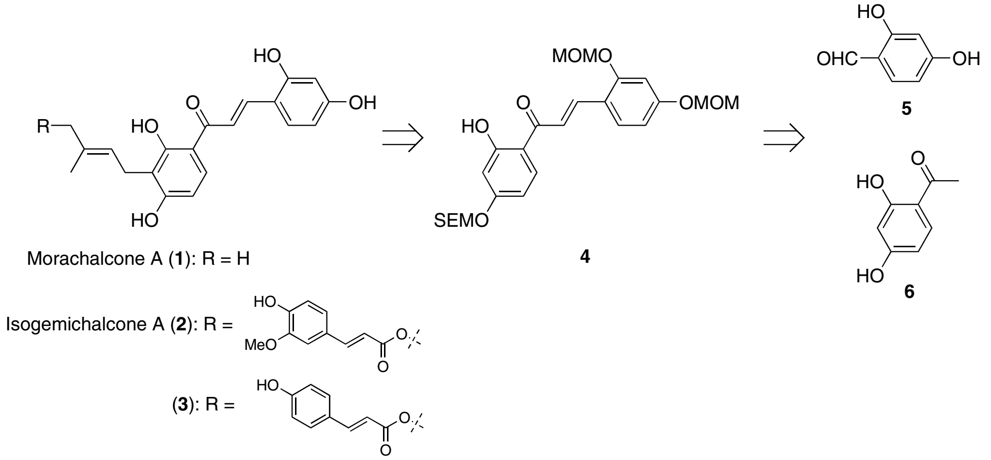


Figure 1. Retrosynthetic scheme of morachalcone A (**1**) and its aromatase inhibitor derivatives (**2**, **3**).

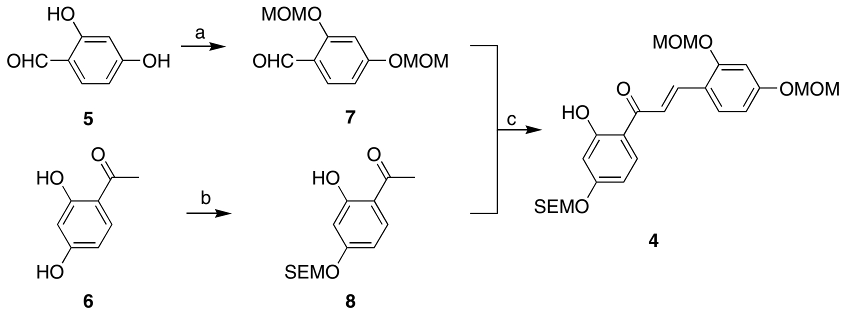
while acetophenone **6** was selectively protected at the 4-position as a SEM ether in 96% yield (Scheme 1). Condensation of **7** and **8** under Claisen–Schmidt conditions[6] provides the desired enone (**4**) in 66% yield after optimization without evidence of the undesired *cis* enone.

The aldol condensation was very sensitive to modification of reaction parameters. A significant excess of KOH (150 equiv) was required to force the reaction to completion. It was noted that the SEM ether was intolerant of prolonged reaction times, while the MOM ether was sensitive to acidic workup. Numerous protection strategies were attempted and the silylethoxymethyl (SEM) and methoxymethyl (MOM) combination provided the best aldol reaction, most other combinations failed to give any useful conversion.

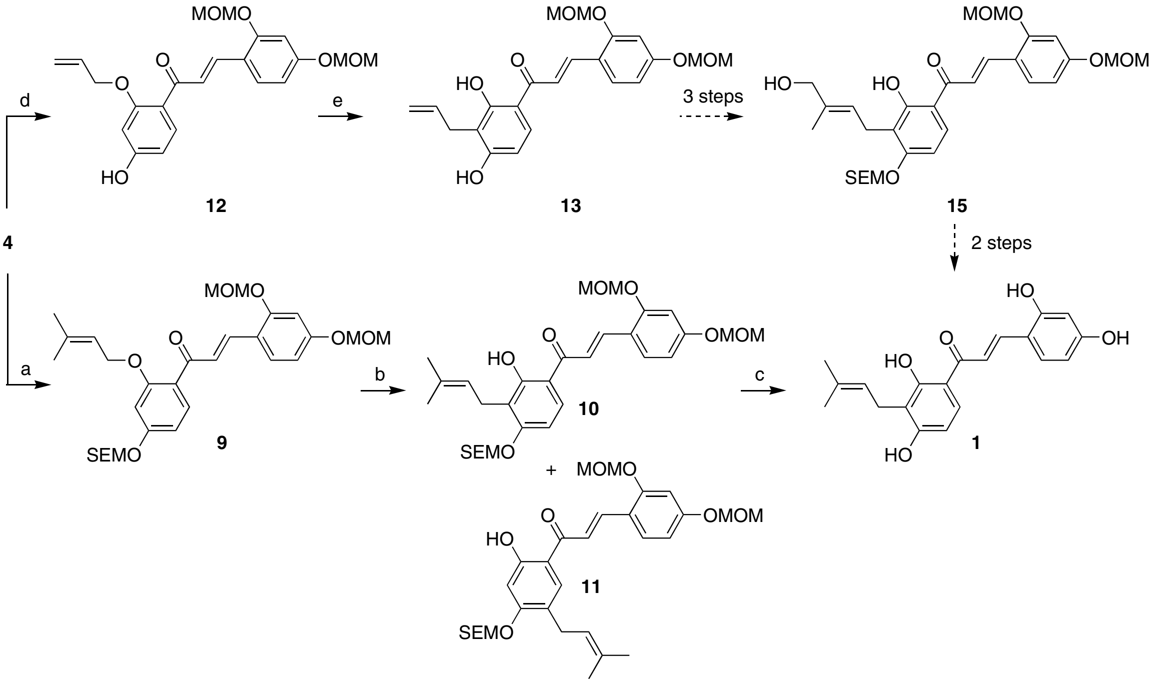
With the core chalcone established, all that remained was the installation of the appropriately functionalized prenyl group. Similarly protected phenols have been prenylated in five steps from phenolic intermediates[7] through *O*-allylation, Claisen rearrangement, ozonolysis, Wittig olefination and reduction (Scheme 2). In our case, ozonolysis was to be avoided due to the presence of the enone. Further, attempts at Claisen rearrangement of allyl ether **12** through heating with *N*,*N*-dimethylaniline at 200 °C gave only a small amount of the desired Claisen product (8% yield) accompanied by ether cleavage and numerous decomposition products. Direct prenylation of the aromatic ring in **4** with prenyl bromide using Friedel–Crafts conditions or aryl anionic quench yielded no product.

Alternatively, numerous steps could be saved by directly installing an *O*-prenyl group that could be converted to the *C*-prenylated chalcone by 1,3-rearrangement (Scheme 2). Furthermore, installation of the unsubstituted prenyl group on the aromatic ring would allow for synthesis of all three natural products, instead of just **2** and **3.** The Claisen route would potentially provide the hydroxylated prenyl group leading to **2** and **3**, but would prohibit synthesis of **10** as an intermediate through the same route.

Prior work has shown that 1,3-rearrangement of *O*-prenylated phenols[8,9] can be achieved with either montmorillonite clay, Florisil® or silica gel. *O*-Prenylation was achieved by reacting **4** with excess prenyl chloride in refluxing acetone. This resulting prenyl ether (**9**) was rearranged[8] to **10** using a Florisil® catalyzed [1,3]-sigmatropic shift to install the *C*-prenyl group [toluene, 100 °C, 10/1 w/w Florisil®]. Some deprenylated (**4**) and *p*-rearranged (**11**) products were also detected in a 2:1:1 ratio of **10**:**11**:**4** as reported by Talamas et al.[8] Although Florisil® catalysis did not prevent formation of these byproducts, the desired isomer **10** was found to be the major product, obtained in 23% isolated yield.



Scheme 1. Synthetic sequence to enone **4**. Reagents and conditions: (a) MOMCl, NaH, THF, 65 °C, 18 h, 82%; (b) SEMCl, DIPEA, CH_2Cl_2, 25 °C, 3 h, 96%; (c) KOH, EtOH, 25 °C, 18 h, 66%.



Scheme 2. [3,3] versus [1,3]-Rearrangement strategies to morachalcone A. Reagents and conditions: (a) prenyl chloride, K_2CO_3, acetone, 65 °C, 18 h, 87%; (b) Florisil®, toluene, 100 °C, 8 h, 23%; (c) HCl, 1:1 *i*-PrOH–THF, 25 °C, 18 h, 46%; (d) allyl bromide, K_2CO_3, acetone, 65 °C, 18 h, 78%; (e) *N*,*N*-dimethylaniline, 200 °C, 18 h, 8%.

The Dauben protocol[9] using montmorillonite clay in benzene gave the desired product as well, but only provided a 1:1:2 ratio of **10**:**11**:**4** in 9% yield of **10**. Silica gel catalysis gave only deprenylated product (**4**). Morachalcone A (**1**) was formed by simultaneous acid catalyzed deprotection of the MOM and SEM ethers in 46% yield.

Current investigations to prepare **2** and **3** from intermediate **10** are underway (Fig. 2). Oxidation[10] with SeO_2 provides the *trans* allylic alcohol (**16**). A unified synthetic pathway consisting of ester formation with the appropriate carboxylic acid and deprotection may allow preparation of all three natural products. Acids could be synthesized in three steps from commercially available hydroxycinnamic acids via esterification, protection as the SEM ethers, and hydrolysis of the ester to the carboxylic acid.

The described method of preparing intermediate **10** has allowed for the synthesis of aromatase inhibitor morachalcone A (**1**) in six steps with a 5.8% overall yield from inexpensive, commercially available phenol reagents. The sequence also has the potential to provide two other potent aromatase inhibitors of natural origin in as little as nine steps each for **2** and **3** from common intermediate **10**. Further modifications in catalyst and reaction conditions are currently being studied for the 1,3-rearrangement that would allow for better selectivity over the undesired *p*-product (**11**) and increase the overall yield significantly. Although the isolated yield of the 1,3-rearrangement is a modest 23%, this pathway has the advantage of avoiding the longer and potentially more problematic Claisen route (Scheme 2). This method also lends itself to the rapid analog synthesis of other isogemichalcone C analogs through reaction with various carboxylic acids.

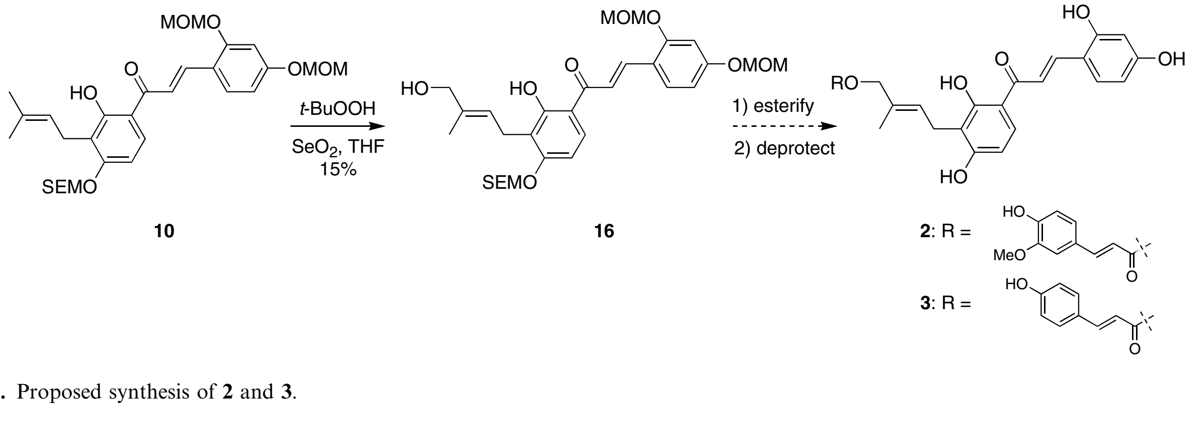


Figure 2. Proposed synthesis of **2** and **3**.

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Supplementary data

Experimental data for compounds **1**, **4**, **7**–**10**, and **16** are included. Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.01.174.

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