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A concise synthesis of rooperol and related 1,5-diarylpent-1-en-4-ynes

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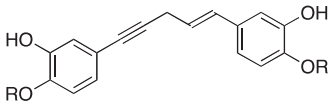
ABSTRACT

Two powerful strategies: rapid construction of allylic alkynoates via cyclopropenium ion chemistry and mild, palladium-catalyzed decarboxylative coupling were employed in a concise, 5-steps synthesis of the natural product rooperol. The overall approach allows the preparation of rooperol analogs in as few as 3 steps.

Extracts of the corm of the African potato (*Hypoxis hemerocallidea*) are widely used in South Africa for a variety of medical conditions.[1] Investigation of the biologically active constituents of *H. hemerocallidea* have led to the isolation and structural elucidation of the major phenolic constituent of this plant, the bis-glucoside hypoxoside (**1**) (Fig. 1).[2] The hypoxoside and its aglycone, rooperol (**2**) were the first natural products reported to possess the unusual 1,5-diarylpent-1-en-4-yne moiety. However, more recently a number of other plant-derived polyphenolic natural products have been reported that possess either this core structure[3] or the related 1,5-diarylpent-4-yne-1,2-diol moiety.[4–6]

These natural products are particularly interesting, as they are all derived from plants that have been used medicinally. For example, rooperol has been reported to possess anticancer, anti-inflammatory, antibacterial, and antioxidant activities.[7–10] Interestingly,



Hypoxoside(1) R = β–D-glucopyranosyl
Rooperol (2): R = H

Figure 1. Structure of the 1,5-diarylpent-1-en-4-yne natural product hypoxoside and its aglycone rooperol.

we recently demonstrated that rooperol inhibits the mitogen-activated protein kinase p38α through a unique mechanism that may account for the anti-inflammatory effects of this natural product.[11]

Despite the promising biological activity of rooperol and related 1,5-diaryl-pent-1-en-4-ynes, only one total synthesis has been reported. Drewes and co-workers prepared rooperol via a low-yielding coupling of a terminal acetylene with an allylic bromide.[12] The challenge with this coupling, and the subsequent low-yielding deprotection step, was attributed to the propensity of the 1-en-4-yne moiety to undergo base-catalyzed isomerization.

In our continuing studies of the p38α kinase inhibition by rooperol and analogs, we set out to develop a more concise and efficient route to this class of natural products. Our goal was to establish a more robust route by avoiding the basic conditions during the construction and deprotection of the 1,5-diaryl-pent-1-en-4-yne system. Here we report a much improved route to rooperol and analogs that employs two powerful strategies: a rapid construction of allylic alkynoates via cyclopropenium ion chemistry (**A**- > **B**, Scheme 1) and a mild palladium-catalyzed decarboxylative sp–sp^3 coupling of these allylic alkynoates to afford the 1,5-diaryl-pent-1-en-4-yne system (**B**- > **C**, Scheme 1). These, together with an improved procedure for deprotection of catechol silylethers, enable a high-yielding, 5-steps synthesis of rooperol and the preparation of rooperol analogs in as few as three steps.

Detty and co-workers have described an interesting approach to phenylpropiolate esters via phenyl-substituted trichlorocyclopropenes **4** (Scheme 2).[13] These are formed by Friedel–Crafts alkylation

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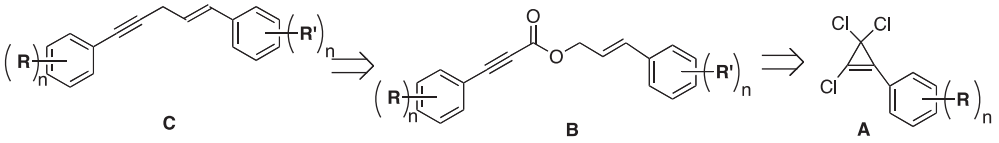
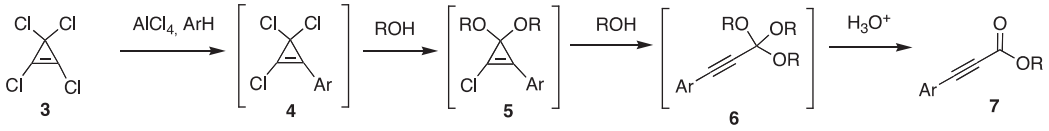


Scheme 1. Retrosynthetic analysis of rooperol and analogs.



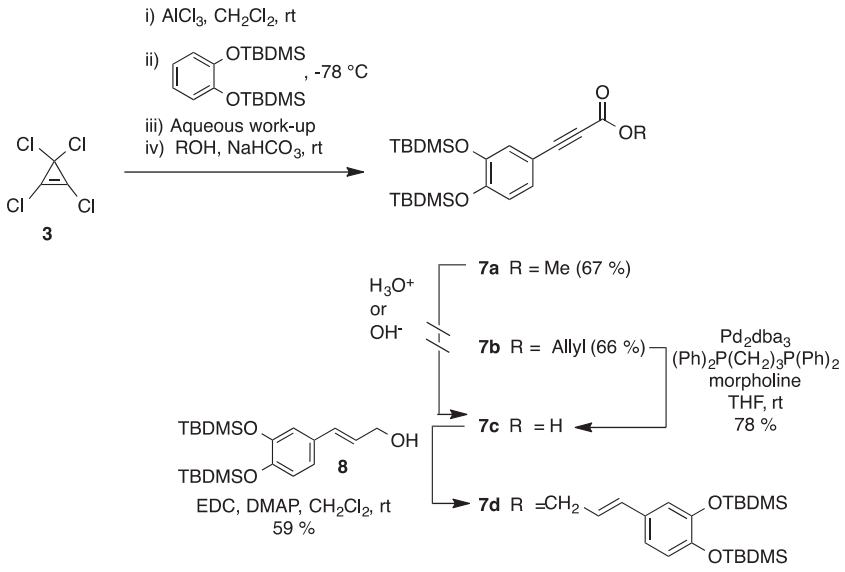
Scheme 2. Cyclopropenium route to arylpropiolate esters.[13]

of electron-rich aromatic compounds by the trichlorocyclopropenium species derived from tetrachlorocyclopropene (**3**). Alcoholysis of cyclopropenes **4** proceeds through proposed intermediate dialkoxycyclopropenes **5**, which undergo ring-opening to afford orthoesters **6**. These can be isolated, or more conveniently hydrolyzed via work-up to provide the esters **7** (Scheme 2).

Although not widely adopted, the approach shown in Scheme 2 has potential advantages to alternative routes to phenylpropiolate esters. In the present case, we sought bis(tert-butyldimethylsilyl)-protected catechol-functionalized phenyl-propiolic esters **B** (Scheme 1). Although tert-butyldimethylsilylethers (TBDMS ethers) are generally considered resistant to deprotection under basic conditions, TBDMS ethers of phenols[14] and catechols[15] undergo deprotection even under relatively mild basic hydrolytic conditions. This lability limited our initial attempts to prepare TBDMS-protected catechol-functionalized phenylpropiolic acid precursors of **B** (see Scheme 3 and discussion, below). Thus, we reasoned that the use of allyl alcohols in the alcoholysis of **4** (Scheme 2), although not reported in the original work, might provide an alternative route to these esters. Use of allyl alcohol should afford allyl phenylpropiolates **7** (R = allyl, Scheme 2) suitable for mild palladium-catalyzed deprotection to the corresponding acids. Alternatively, the required cinnamyl esters **B** (Scheme 1) might be directly obtained from the arylcyclopropenes **A** by employing cinnamyl alcohols in the alcoholysis. Since allyl and cinnamyl phenylpropiolates are versatile synthetic intermediates in their own right,[16–20] this strategy for their rapid construction could have even broader applications than that described here for the synthesis of rooperol and analogs.

In a single synthetic transformation, tetrachlorocyclopropene in the presence of $AlCl_3$ was allowed to react with bis(TBDMS)-protected catechol at −78 °C. Following a rapid aqueous work-up, the crude aryltrichlorocyclopropene was treated with excess methanol and $NaHCO_3$. After acidic workup and chromatography, the methyl alkynoate **7a** was isolated in moderate yield (Scheme 3). However, attempts to hydrolyze **7a** under aqueous acidic or basic conditions met with failure due to the lability of the catechol silyl ethers (see above). In contrast, when the same procedure was carried out with allyl alcohol in place of methanol, the allyl ester **7b** was obtained (Scheme 3).[21] Deallylation of **7b** under conditions reported by Sato and co-workers to limit subsequent decarboxylation of the carboxylic acid (morpholine in the presence of catalytic Pd_2dba_3/1,3-diphenylphosphopropane)[22] afforded the carboxylic acid **7c** in good yield. The requisite allylic alkynoate **7d** was prepared by standard esterification of the acid **7c** with the functionalized cinnamyl alcohol **8**,[23] prepared in two steps from caffeic acid.

A more concise preparation of **7d** was attempted by repeating the arylcyclopropene alcoholysis by employing the alcohol **8** in place of allyl alcohol (Scheme 4). This failed to afford **7d**; instead the ether **9** was obtained along with more polar, uncharacterized material. Since the alcoholysis is carried out in the presence of



Scheme 3. Synthesis of functionalized phenylpropiolate esters.