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

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Keywords: Cyclopropenium Palladium-catalyst Decarboxylative coupling Catechol Desilylation Norlignans 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.

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Extracts of the corm of the African potato (*Hypoxis hemerocallidea*) are widely used in South Africa for a variety of medical conditions.<sup>1</sup> 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).<sup>2</sup> 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<sup>3</sup> or the related 1,5-diarylpent-4-yne-1,2-diol moiety.<sup>4-6</sup>

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.<sup>7–10</sup> Interestingly,



Hypoxoside(1)  $R = \beta$ -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.

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we recently demonstrated that rooperol inhibits the mitogenactivated protein kinase  $p38\alpha$  through a unique mechanism that may account for the anti-inflammatory effects of this natural product.<sup>11</sup>

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.<sup>12</sup> 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 p38 $\alpha$  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<sup>3</sup> 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).<sup>13</sup> 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.<sup>13</sup>

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<sup>14</sup> and catechols<sup>15</sup> 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,<sup>16–20</sup> 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<sub>3</sub> 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<sub>3</sub>. 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).<sup>21</sup> 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)<sup>22</sup> 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**,<sup>23</sup> 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

![](_page_1_Figure_10.jpeg)

Scheme 3. Synthesis of functionalized phenylpropiolate esters.

![](_page_2_Figure_1.jpeg)

Scheme 4. Attempted preparation of 7d directly from 3 affords instead the ether 9, possibly via an alternative attack (blue arrows) on a cyclopropenone ketal intermediate.

![](_page_2_Figure_3.jpeg)

Scheme 5. Direct synthesis of cinnamyl phenylpropiolate esters.

excess base, it is unlikely that **9** forms via simple acid-catalyzed etherification of **8**. Rather, **9** may be derived from a cyclopropenone ketal intermediate (Scheme 4) via an attack by **8** on one of the

cinnamyl  $sp^3$  carbons, as opposed to attack at the ketal carbon to afford the orthoester precursor to **7d**.

In contrast to the case of **8** (Scheme 4), use of cinnamyl alcohol or 3,4-difluorocinnamyl alcohol in the alcoholysis step directly affords the desired esters **7e** and **f** from tetrachlorocyclopropene (Scheme 5). In these cases, small amounts of the ethers analogous to **9** are observed in the <sup>1</sup>H NMR spectra of the crude reaction mixtures. Interestingly, the product **7e** derived from cinnamyl alcohol containing a small amount of 3-phenylpropanol (ca. 5%) was enriched in the 3-phenylpropanol ester (ca. 10–15%). This enrichment may be due to a process analogous to that shown in Scheme 4, in which the cinnamyl groups of an intermediate ketal are preferentially attacked as compared to the alkyl groups derived from the saturated alcohol. This would lead to enrichment of the saturated groups in the resulting orthoesters, and thus the final ester product.

Next, a mild and base-free palladium-catalyzed decarboxylative coupling recently reported by Tunge and co-workers<sup>24</sup> was employed to construct the pent-1-en-4-yne system. Palladium-catalyzed decarboxylative coupling of esters **7d–f** proceeded in the presence of 5 mol % of Pd[P(Ph)<sub>3</sub>]<sub>4</sub> in THF at 80 °C to give

![](_page_2_Figure_9.jpeg)

Scheme 6. Palladium-catalyzed decarboxylative coupling and subsequent deprotection.

![](_page_3_Figure_1.jpeg)

Scheme 7. Synthesis of a rooperol hydroquinone analog.

protected rooperol **10d**<sup>12</sup> and analogs **10e** and **f** in good yield.<sup>25</sup> We attempted the desilylation of these protected catechols by treatment with TBAF in THF at -78 °C, but in accord with previous work,<sup>12</sup> this afforded mostly polymeric material. However, a recently reported improved procedure for the deprotection of particularly labile silylated polyphenols was much more effective.<sup>26</sup> Thus, treatment of **10d**–**f** in DMF with KF and HBr/AcOH afforded rooperol (**2**), 3,4-bis(dehydroxy)rooperol **11e**,<sup>27</sup> and the difluororooperol analog **11f** in good yield (Scheme 6).

In order to probe the generality of this approach, we also prepared the A-ring hydroquinone analog of rooperol (Scheme 7). Addition of the bis(tert-butyldimethylsilyl)-protected hydroquinone to the cyclopropenium species formed from tetrachlorocyclopropene and aluminum chloride in dichloromethane, followed by rapid aqueous work-up and alcoholysis with excess allyl alcohol afforded the allyl ester **16**. Palladium-catalyzed deallylation and subsequent coupling with the functionalized cinnamyl alcohol **8** gave the ester **19**, which underwent smooth palladium-catalyzed decarboxylative coupling to afford the protected pent-1-en-4-yne **19**. Deprotection of **19** employing the same conditions as above produced the hydroquinone rooperol analog **20**.

In conclusion, a concise synthesis of rooperol in 5 steps and 17% overall yield from tetrachlorocyclopropene was accomplished. This is an improvement from the previously published route that required 9 total steps and proceeded in 4.1% overall yield from ethyl caffeate.<sup>12</sup> This improved route employs a cyclopropenium

approach to allyl arylpropiolates, which undergo palladium-catalyzed deallylation (in the presence of base) or decarboxylative coupling (under neutral conditions). This same approach also afforded the rooperol hydroquinone analog **20**. In some cases, this general approach allows an even more concise route to rooperol analogs; analogs **11e** and **f** were prepared in just 3 steps. Thus, the approach we report here has the potential to greatly facilitate the biological study of rooperol and analogs. Moreover, the direct preparation of allyl and cinnamyl arylpropiolates employed here is noteworthy, as these are versatile synthetic intermediates. Biochemical and biological evaluation of these analogs is currently under investigation.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10. 138.

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- General Procedure: A mixture of 290 mg (2.17 mmol) AlCl<sub>3</sub> and 5 mL  $CH_2Cl_2$  was 21 stirred at room temperature under argon while 376 mg (2.1 mmol) of tetrachlorocyclopropene was added dropwise. The resulting suspension was stirred at room temperature for an additional 15 min and then cooled in a dry

ice/acetone bath. A solution of 843 mg (2.49 mmol) of 1,2-bis((tertbutyldimethyl-silyl)oxy)benzene in 3 mL of CH2Cl2 was added dropwise, and then the ice bath was removed. After the reaction mixture had warmed to room temperature, it was placed in a 50 °C oil bath until the evolution of HCl subsided (ca. 10 min). After cooling on ice, the reaction mixture was treated with 10 mL of ice cold water. This was extracted  $2 \times$  with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers dried over MgSO4 and filtered into a flask containing 856 mg (14.7 mmol) of allyl alcohol. After the addition of 2.55 g NaHCO<sub>3</sub>, the mixture was stirred at room temperature for 30 min. The reaction mixture was filtered, warmed in a 50 °C oil bath for ca. 5 min, and then 15 mL of 1 N HCl was added. The layers were separated and the organic layer was washed once with dilute NaHCO3 and dried over Na2SO4. The residue upon filtration and evaporation of the solvent was subjected to flash chromatography (0, 2.5% EtOAc/Hexane) to afford 7b as a slightly yellow oil (627 mg, 1.40 mmol, 66%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.10 (1H, dd, J = 8.3, 2.0 Hz), 7.04 (1H, d, J = 2.0 Hz), 6.79 (1H, d, J = 8.3 Hz), 5.97 (1H, ddt, HJ = 17.2, 10.4, 5.9 Hz), 5.40 (1H, dm, J = 17.2 Hz), 5.30 (1H, dm, J = 10.4 Hz), 4.72 (2H, dm, J = 5.9 Hz), 0.98 (9H, s), 0.97 (9H, s), 0.21 (6H, s), 0.20 (6H, s). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  154.0, 150.3, 146.9, 131.3, 127.5, 125.5, 121.1, 119.3, 111.9, 87.5, 79.5, 66.4, 25.8 (2C),18.5, 18.4, -4.1, -4.2. IR (thin film): 3020, 2954, 2931, 2869, 2860, 2213, 1704, 1508 cm^{-1}. HRMS (ESI\*) calcd for  $C_{24}H_{38}NaO_4Si_2~(M+Na)^*$  469.2201, found 469.2196

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- General Procedure: A solution of 134 mg (0.171 mmol) of ester 7d in 2.5 ml of freshly-distilled THF was transferred under argon to a reaction tube containing 10 mg (0.0086 mmol) of Pd[P(Ph)<sub>3</sub>]<sub>4</sub> and the tube was sealed. After heating for 4 h in a 80 °C oil bath, the contents of the tube were transferred to a roundbottomed flask with EtOAc, the solvent evaporated and the residue was subjected to flash chromatography (0-1% EtOAc/hexanes) to afford 10d as a yellow oil (105 mg, 0.142 mmol, 83%). <sup>1</sup>H NMR and IR matched that previously reported.<sup>12</sup> <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  147.3, 146.8, 146.6, 146.4, 130.9, 125.3, 124.3, 122.4, 121.0, 120.9, 119.6, 118.9, 116.5, 105.0, 85.2, 82.4, 26.0, 25.9, 22.9, 18.5, 18.4, -4.1. HRMS (ESI<sup>+</sup>) calc for C<sub>41</sub>H<sub>71</sub>O<sub>4</sub>Si<sub>4</sub> (MH)<sup>+</sup> 739.4424, found 739.4422.
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