

## Directing Tandem Catalyzed Reactions as an Approach to Furans and Butenolides

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The widespread occurrence of oxygen heterocycles in nature and their relationship to furanose derivatives make their easy availability by synthesis important. In searching for new strategies based upon the concept of simple additions,<sup>1</sup> we turned our attention to the concept of a butenolide synthesis based upon a palladium-catalyzed conjugate addition of terminal alkynes to  $\gamma$ -hydroxyalkynoates.<sup>2</sup> While the Michael reaction of stabilized carbon nucleophiles constitutes one of the fundamental C–C bond forming processes, this process does not generally extend to acetylide anions.<sup>3</sup> Effecting such additions by use of a transition metal catalyst may have the advantage of (1) extending the reaction to acceptors that may not otherwise participate, (2) controlling stereochemistry (geometry) where applicable, (3) promoting further useful transformations of the initial adducts, and (4) enhancing synthetic efficiency by not requiring stoichiometric amounts of reagents like bases or metals. We wish to record protocols whereby the addition of terminal alkynes to  $\gamma$ -hydroxyalkynoates catalyzed by palladium can be directed to form either butenolides (eq 1, path a)<sup>4,5</sup> or furans (eq 1, path b).<sup>6</sup>

With an eye to developing general methodology for ynediene natural products,<sup>7</sup> we explored the addition of **1a** outlined in eq 1 as a route to butenolide **4a**. Exposing the two reactants to 2 mol % palladium acetate and 2 mol % tris(2,6-dimethoxyphenyl)phosphine<sup>8</sup>(TDMPP) in THF did indeed produce **4a**<sup>9</sup> but also a second product readily identified as furan **5a**<sup>9</sup> by its spectroscopic properties. To explore what role, if any, the presence of a hydroxyl group in the donor alkyne played in facilitating furan formation and to determine the parameters to promote furan formation, we turned to a simpler system, **1b** (eq 1). Most revealing was the effect of the ratio of ligand to palladium salt on this process. In this case, lactonization of the initial adduct **2b** to **4b** appears to be quite slow and the preferred cyclization path produces the furan **5b**. Treatment under the above conditions gives mostly the initial adduct as well as furan. Performing the reaction in benzene saw more conversion of the initial adduct **2b** to a mixture of isofuran **3b**<sup>10</sup> and furan **5b**. To establish whether the rather basic phosphine TDMPP was promoting furan formation, its ratio relative to palladium acetate was increased. However, the net effect was a strong inhibition of cyclization of **2b**. Quite the contrary, increasing the amount of palladium acetate relative to TDMPP dramatically improved the furan formation. Thus, using a 1:2 or preferably 2:5 TDMPP:Pd(OAc)<sub>2</sub> ratio effects complete addition and cyclization to **3b** and **5b**. The tautomerization of the isofuran is completed upon addition of DBU at this point. These results implicate unligated palladium acetate as the preferred catalyst for the cyclization of the initial adduct.

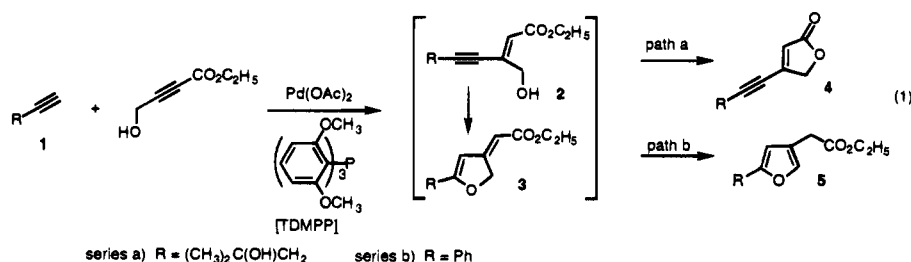
Adopting as a standard protocol addition of 1 equiv of alkyne and 1 equiv of alkynoate to 2 mol % TDMPP, 5 mol % Pd(OAc)<sub>2</sub> in PhH at ambient temperature followed by 0.75–1.5 equiv of DBU gave furan **5b**<sup>9</sup> in 87% yield after direct column chromatography of the reaction mixture. This same protocol gave furan **5a** in 73% yield. Equations 2 and 3 provide further examples of the synthesis of furans **6**,<sup>9</sup> **7**,<sup>9</sup> and **9**.<sup>9</sup>

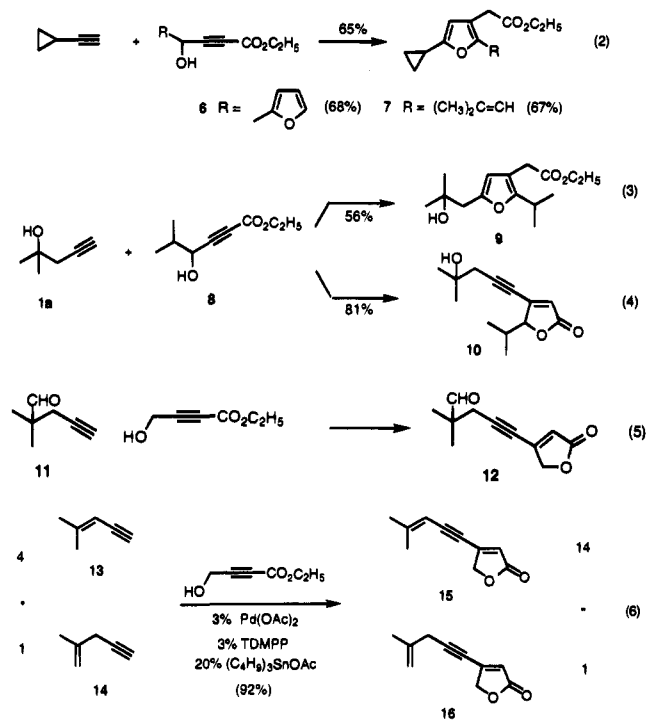
Can the initial adduct be directed toward butenolide formation at the expense of furan formation? Since uncomplexed palladium acetate enhances furan formation, addition of a base like triethylamine may reduce the Lewis acidity of palladium acetate as well as serve as a general base catalyst for lactonization. Indeed, in the reaction of donor alkyne **1a** and ynoate **8** with TDMPP using a 1:1 THF:(C<sub>2</sub>H<sub>5</sub>)<sub>3</sub>N mixture as solvent, furan formation was completely suppressed and butenolide **10** was isolated in 81% yield (eq 4). However, in a number of other cases, significant amounts of furan still formed under these conditions.

A much more effective approach involved addition of a catalytic amount (10–40 mol %) of tri-*n*-butyltin acetate to serve as a transesterification catalyst. A standard operating procedure which involved adding 20 mol % of tri-*n*-butyltin acetate to 3 mol % palladium acetate and 3 mol % TDMPP in THF followed by 1 equiv of hydroxy ynoate and 1 equiv of terminal alkyne for 16 h at room temperature followed by direct column chromatography of the reaction mixture was adopted. In this way, phenylacetylene (**1b**) added to ethyl 4-hydroxybutynoate to give butenolide **4b**<sup>9</sup> in 58% yield. A particularly interesting example illustrating the chemoselectivity of this process is the addition of donor alkyne **11** (equiv 5). Only addition to the ynoate to give butenolide **12**<sup>9</sup> is observed without any need to protect the normally very reactive aldehyde.

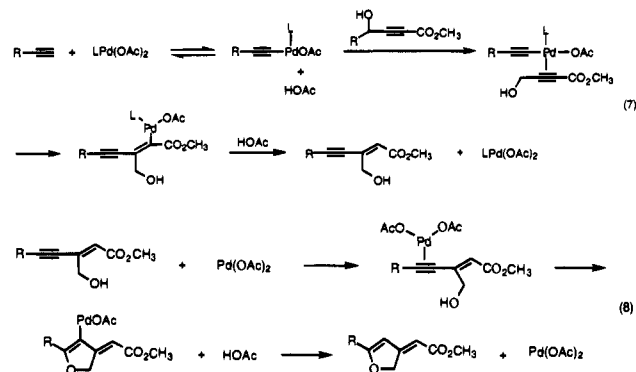
The utility of this protocol was examined in the context of a synthesis of a simple ynediene natural product, cleviolide (**15**),<sup>11,12</sup> which by virtue of the sensitivity of the polyunsaturation within a small molecular framework demands very mild methods. Interestingly, utilizing an excess of a 4:1 ratio of the conjugated and unconjugated enynes<sup>12</sup> **13** and **14** with ethyl 4-hydroxybutynoate gave a 92% yield of a 14:1 ratio of cleviolide (**15**) to isocleviolide (**16**) (eq 6) from which pure cleviolide can be crystallized. Crystalline cleviolide, mp 60–62 °C, has spectral properties in full accord with the reported values. The kinetic enrichment observed in this reaction derives from the higher reactivity of the conjugated enynes as donors compared to simple terminal alkynes, a qualitative observation first made in comparing the reactions of phenylacetylene and 1-ethynylcyclohexene to other donors. The rate difference between **13** and **14** may be estimated to be 3.5:1, a remarkable difference given the nature of the reaction and the closeness of the two structures. This also constitutes a formal synthesis of (*E*)- and (*Z*)-scobinolide.<sup>12</sup>

Thus, the addition of terminal alkynes to  $\gamma$ -hydroxy ynoates may be readily directed to form either furans in two tandem palladium-catalyzed reactions or butenolides in a palladium–tin cocatalyzed event. The ease of availability of  $\gamma$ -hydroxyalkynoates<sup>13</sup> makes such methods particularly convenient. The mechanism of these reactions<sup>2c</sup> remains to be clarified. At this





point, we prefer a route as outlined in eq 7 for the addition reaction and eq 8 for furan formation.<sup>6</sup> The regioselectivity



better supports a carbapalladation compared to a hydropalladation as the first step. The rate differential between **13** and **14** also is in better accord with this proposal since we previously have shown that insertion into the C–H bond is fast and reversible.<sup>14</sup> This extraordinary selectivity bodes well for chemoselectivity in other palladium-catalyzed cross couplings of terminal alkynes. Both of these mechanisms suggest opportunities for further elaboration involving the vinylpalladium intermediates. The efficiency of this chemistry is illustrated by the very simple synthesis of the sensitive ynediene cleviolide by a simple addition which contrasts sharply with the only previous synthesis<sup>12</sup> and opens an opportunity of utilizing this strategy for other members of this class such as the cytotoxic caulerpenynes,<sup>7</sup> whose low natural abundance (0.0021% of the lyophilized weight of the seaweed source) necessitates total synthesis for biological evaluation.

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**Supporting Information Available:** Characterization data for **4–7**, **9**, **10**, **12**, and **15** and an experimental procedure for the preparation of cleviolide (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(10) Assigned by spectral data on crude reaction mixture. IR (film): 1752, 1674, 1618, 1601, 1587, 1566  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (200 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  7.5 (m, 2H), 7.0 (m, 3H), 5.8 (t,  $J = 3$  Hz, 1H), 5.7 (s, 1H), 5.6 (d,  $J = 3$  Hz, 2H), 4.1 (q,  $J = 7.1$  Hz, 2H), 1.05 (t,  $J = 7.1$  Hz, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.7, 167.9, 162.8, 130.8, 129.4, 128.6, 126.4, 102.0, 100.6, 77.4, 59.5, 14.5.

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