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Metal-catalyzed coupling reactions on an olefin template: the total synthesis of Bupleurynol

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Abstract—The naturally occurring polyacetylene Bupleurynol was synthesized in a convergent and stereospecific manner using a series of metal-mediated cross-coupling reactions. The synthesis demonstrates the utility of using a di-functional olefin template for the stereospecific synthesis of a disubstituted alkene product and its elaboration to a natural product target.

The polyacetylene Bupleurynol, or (2*Z*,8*E*,10*E*)-2,8,10-heptadecatriene-4,6-diyn-1-ol (**1**, Fig. 1), was isolated originally in 1987 in China by Zhao and co-workers from the perennial plant *Bupleurum longiradiatum*.[1] However, it only came to the attention of the West when Barrero and colleagues isolated the polyacetylene from *Bupleurum acutifolium*, growing in Spain.[2] The *Bupleurum* species of plant has long been used in traditional folk medicine preparations, having potent, and sometimes toxic properties.[1,2] A great deal of the biological activity associated with this, and similar compounds is believed to be attributed to their polyacetylenic substructure.

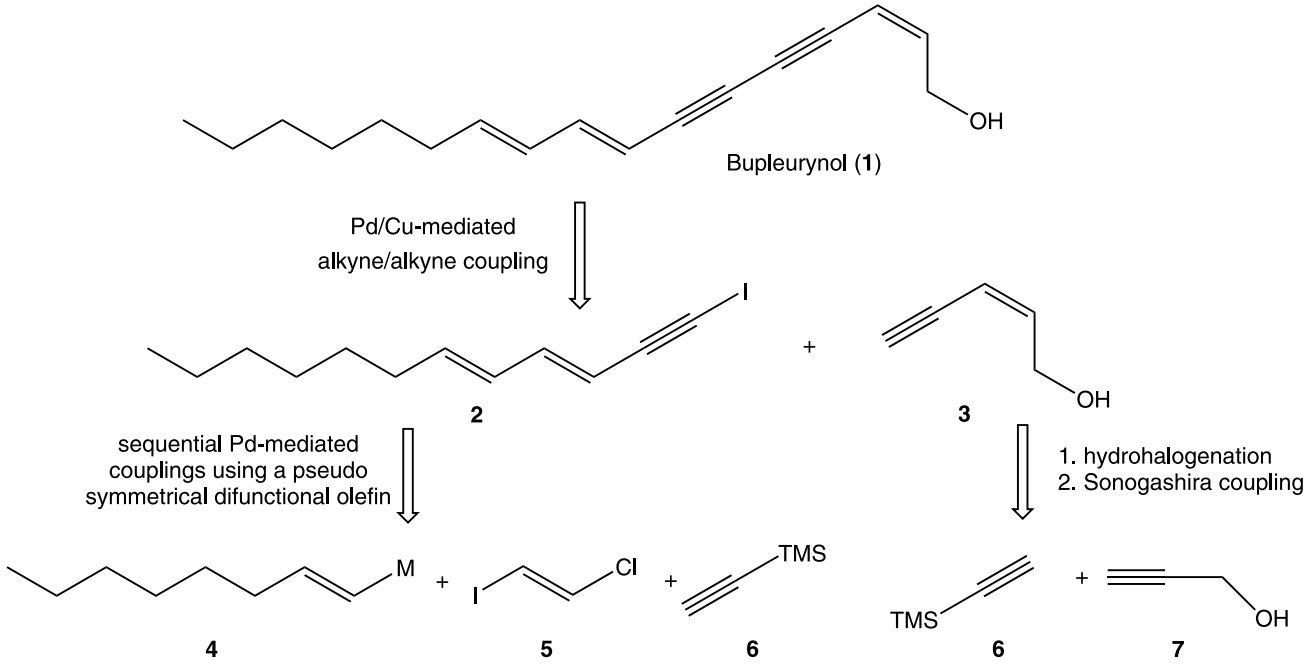

Figure 1. Bupleurynol: its structure and retrosynthetic analysis.

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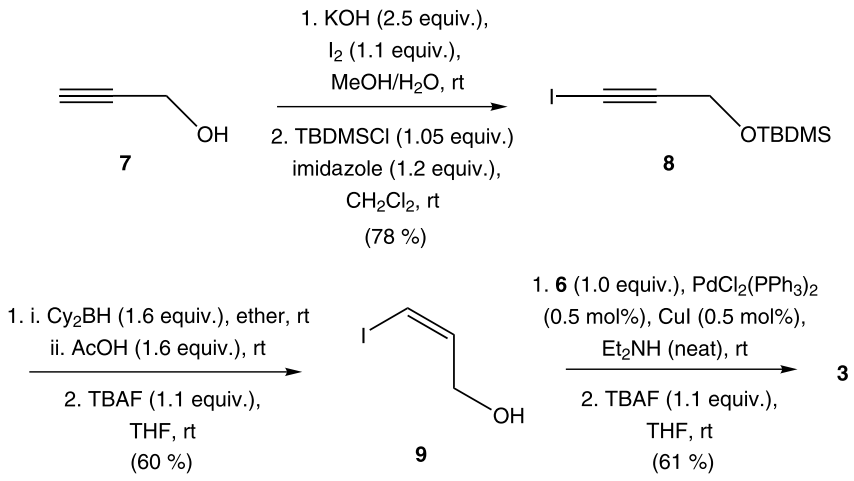


Scheme 1.

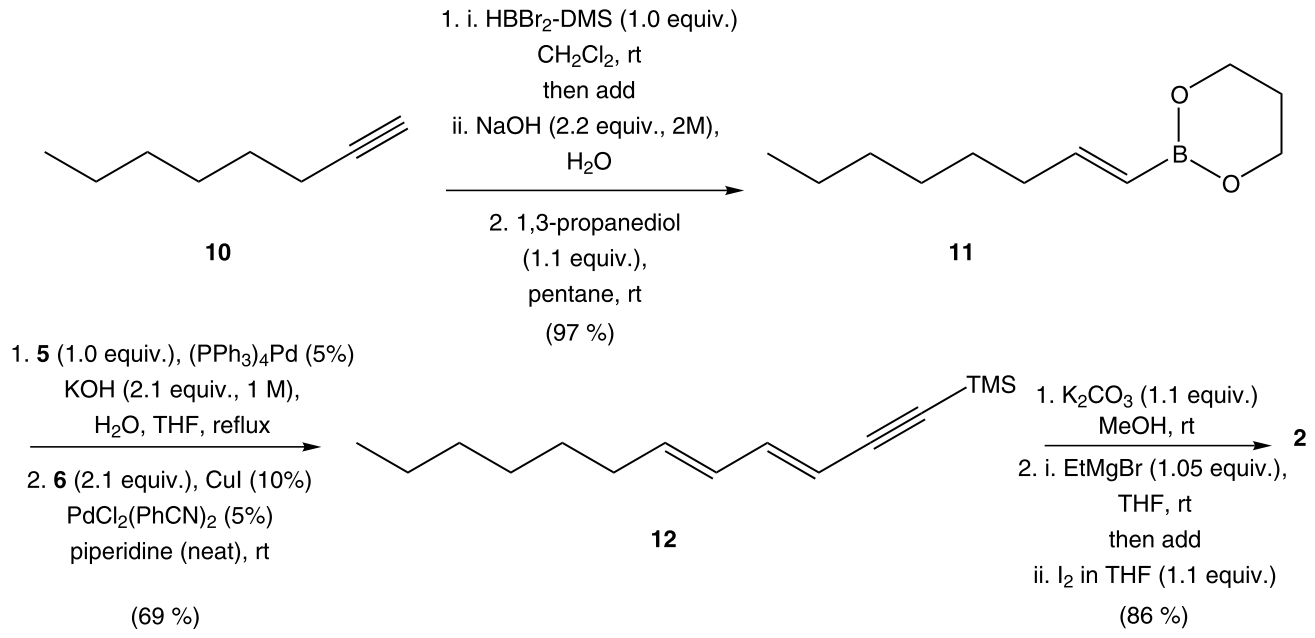
Bupleurynol is characterized by a fully conjugated system consisting of two alkynes and three olefins, the *E*/*Z* geometry of which is rigorously defined. We saw this compound as an opportunity to demonstrate the utility of an olefin template, such as (*E*) 2-iodo-1-chloroethylene (**5**),[3] used in the stereodefined synthesis of disubstituted olefins.[4] In this strategy, poly functionalized olefin building blocks (templates) are used whereby Pd can selectively and sequentially activate these halides (or the corresponding organometallic moieties) whose activities are electronically and/or sterically differentiated. Thus, as demonstrated in Figure 1, the synthesis of **1** can be realized entirely by an ordered sequence of transition metal-mediated coupling reactions of simple compounds, all of which are commercially available or obtainable in one simple synthetic transformation.[5] Herein we describe the first total synthesis of Bupleurynol (**1**) in a convergent and stereospecific manner.

Construction of the right-hand piece **3** began from propargyl alcohol. As shown in Scheme 1, iodination at the terminal acetylenic position of **7** was followed by reduction. Hydroboration of 3-iodo propargyl alcohol actually proceeded well with an excess of the boron reagent.[6] However, byproducts of the cyclohexane ligand co chromatographed and co distilled with the desired product under all conditions tried, thus we opted to protect the alcohol to make the separation more facile.[7] Hydroboration/protonolysis[8] and deprotection gave **9**, which was followed by Sonogashira coupling[9] with **6**, that upon deprotection provided **3**. The TMS group can be removed during the work up as well, thus eliminating one step. In this instance, the TMS group is not a protecting group, but rather is required for ease of handling (i.e. acetylene is a gas).

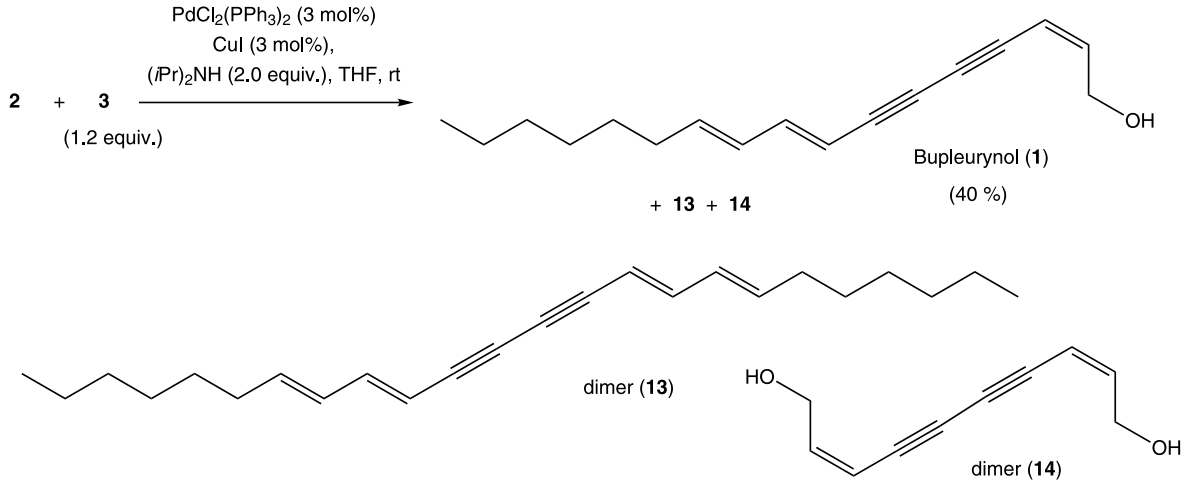
1-Octyne (**10**) was regioselectively hydroborated with dibromoborane and hydrolyzed in situ to the boronic acid that was then converted directly to the borate ester (**11**, Scheme 2). Although the corresponding boronic acid cross coupled well enough with **5** in the presence of a Pd catalyst, the fact that the free acid existed in equilibrium with the cyclic trimer meant that stoichiometry could not be controlled as accurately as desired. Compound **11** was coupled cleanly at the iodide site of **5**, the selectivity of which is due to the weaker C–I bond. However, while a C–Cl bond activates slowly as a coupling partner in such reactions, it is much more reactive in alkyne-related coupling reactions, something that has been observed by others.[10] Thus, Sonogashira coupling with **6** produced **12** that, upon removal of the TMS group and iodination, completed the synthesis of the left-hand piece.

The final alkyne/alkyne coupling was not as straightforward to carry out operationally as it might appear at first glance.[11] The desired coupling between **2** and **3** is complicated by two competing dimerization processes between the starting materials leading to the formation of **13** and **14**, respectively (Scheme 3). The dimerization of **2** is likely to involve Pd whereas the dimerization of simple terminal alkynes by the Cu is known to be a competing process in Sonogashira coupling reactions.[12] When **2** and **3** were used in this reaction in a ratio of 1:1.2, **1**[13] was obtained in 40% yield and dimers **13** and **14** accounted for the remainder of the mass balance. Presumably, oxidative addition of alkynyliodide **2** was the fastest event in the reaction flask and self coupling (dimer formation) and cross coupling with **3** were somewhat competitive processes. Once all of **2** was gone, the only reaction possible for **3** is dimerization.

In summary, we have developed and completed a synthetic route for the total synthesis of Bupleurynol. This synthesis is based on a modular approach comprised of individual building blocks that were all assembled using Pd catalysis. This represents the first synthesis of this highly conjugated structure.



Scheme 2.



Scheme 3.

Acknowledgements

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13. Here are representative spectra for compound **1**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.71 (dd, $J=10.8$, 15.6 Hz, 1H), 6.23 (dt, $J=5.9$, 11.2 Hz, 1H), 6.11 (dd, $J=$ 11.2, 14.8 Hz, 1H), 5.89, dt ($J=7.2$, 14.8 Hz, 1H), 5.68 (d, $J=11.2$ Hz, 1H), 5.56 (d, $J=15.6$ Hz, 1H), 4.43 (dd, $J=6.0$, 6.0 Hz, 2H), 2.12 (dt, $J=7.2$, 7.2 Hz, 2H), 1.38 (m, 2H), 1.28 (m, 6H), 0.87 (t, $J=6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT sequence: (+) evens up, (–) odds down): 145.7 (–), 144.9 (–), 40.6 (–), 129.5 (–), 109.7 (–), 107.1 (–), 83.1 (+), 79.9 (+), 77.6 (+), 75.1 (+), 61.2 (+), 32.9 (+), 31.7 (+), 28.9 (+), 28.8 (+), 22.6 (+), 14.0 (–); IR (neat): 3337 cm^{-1}; HRMS (CI) m/z calcd for $C_{17}H_{22}O$: 242.1671. Found: 242.1657.