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Use of Olefin Templates in Queued Chemical Transformations Using Late Transition Metal Catalysis. Total Synthesis of *cis* and *trans* Bupleurynol via a Single Multireaction Sequence

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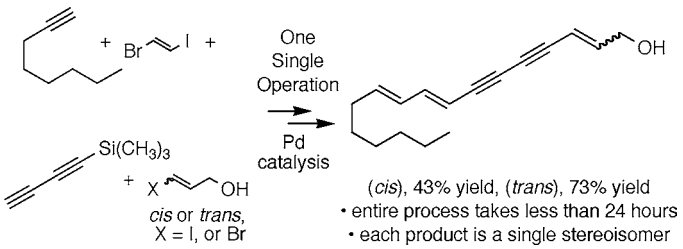
ABSTRACT



1-Bromo-2-iodoethylene (9) was used as a central, pseudosymmetric building block for the fully convergent and modular synthesis of two related natural products, *cis* (1a) and *trans* (1b) bupleurynol. In doing so, a 9-step synthesis of 1a (reported previously) has been vastly truncated to one single operation by using queued cross-coupling reactions with Pd catalysis, negating the need for any protecting group chemistry.

In total synthesis there are a number of criteria that have been recognized as being major contributors to the overall perceived effectiveness, efficiency, or elegance of a given synthetic approach. These include the number of synthetic procedures or steps, overall yield, availability of starting materials, safety, environmental concerns, and cost.[1] Although it is difficult for any given synthesis to optimize simultaneously all of these parameters, chemists still strive to meet as many of these criteria as possible.

We[2] and others[3] have been developing a convergent and modular approach to synthesis with the design and use of polyfunctional olefinic building blocks (olefin templates). Here, a small olefin unit is decorated with a variety of halide and/or organometallic moieties that can be activated selectively and sequentially by transition metal catalysis and converted to the final olefin-containing product by a series of coupling reactions. When the olefin is central in the target,

(1) For philosophical discussions pertaining to chemical synthesis, see: (a) Wender, P. A.; Miller, B. Toward the Ideal Synthesis: Connectivity Analysis and Multi-Bond Forming Processes. In *Organic Synthesis: Theory and Application*; Hudlicky, T., Ed.; JAI Press: Greenwich, 1993; Vol. 2, pp 27−66. (b) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley and Sons: New York, 1989.

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(3) (a) Ratovelomanana, V.; Guillerm, D.; Limstrumelle, G. *Tetrahedron Lett.* **1984**, *25*, 6001−6004. (b) Ratovelomanana, V.; Limstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315−318. (c) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921−6923. (d) Hyuga, S.; Chiba, Y.; Yamashina, N.; Hara, S.; Suzuki, A. *Chem. Lett.* **1987**, 1757−1760. (e) Hyuga, S.; Yamashina, N.; Hara, S.; Suzuki, A. *Chem. Lett.* **1988**, 809−812. (f) Shair, M. D.; Yoon, T.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755−3756. (g) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419−4420. (h) Qian, M.; Huang, Z.; Negishi, E.-i. *Org. Lett.* **2004**, *6*, 1531−1534.

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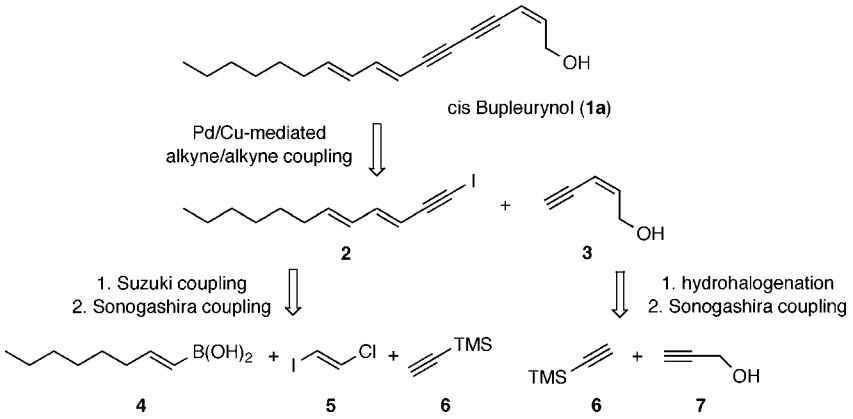


Figure 1. Retrosynthetic approach to *cis*-bupleurynol (**1a**) using *trans*-1-chloro-2-iodoethylene (**5**) as a central olefin template and Pd catalysis.

the approach offers considerable convergency. Further, the specificity of late transition metals for soft coordinating groups (e.g., olefins or alkynes) often negates the need for protecting group chemistry. The generality of cross-coupling reactions provides a high degree of modularity, meaning that one single template is very likely to work in a variety of coupling reactions to produce a large number of chemical structures. Further, olefins themselves are substrates for an even wider array of reactions, and therefore the diversity of chemical structures that can be approached employing such a strategy is almost without limit.[4] Because the same catalyst can be used for a number of coupling procedures, the possibility exists to compress a number of couplings into a single synthetic operation, greatly truncating the synthesis and enhancing efficiency.

Recently, we reported the synthesis of *cis* bupleurynol (**1a**) using 1-chloro-2-iodoethylene (**5**) as the primary building block, or template, in a 9-step procedure in 6% overall yield, and the retrosynthetic approach is outlined in Figure 1.[5] All of the key bond-forming events were catalyzed by Pd, leading to the formation of product as a single stereoisomer.

We revisited the synthesis of this **1a** and redesigned the method in such a way as to heighten the convergency of the approach. At the same time, we sought to maximize the utilization of the Pd catalyst by employing it for multiple couplings in a series of queued transformations (i.e., one-pot) with the general goal of significantly reducing the step count and time, thus improving synthetic efficiency and, ideally, the overall yield.

Key to this new synthesis of **1a** was to try to position the olefin template more centrally in the approach, which is consistent with the philosophy of the template strategy (vide supra).[2] To do so, we had to have the diyne segment intact because our previous approach was more linear than desired as a result of the additional steps involved in the alkyne/alkyne coupling itself and the removal of the associated TMS groups.[5a] Further, the alkyne/alkyne coupling had some selectivity issues associated with it that led to homodimer formation of both **2** and **3**. Another concern was that the formation of the en−yne bond in a fragment such as **2** required anhydrous conditions, so the Suzuki−Miyaura coupling[6] at the other end of the template had to be rethought. With these concerns in mind, the overall synthesis that resulted is outlined in Scheme 1.

Deprotonation of trimethylsilylbutadiyne (**8**) and transmetalation from Li to Zn produced the requisite organometallic coupling partner for a Negishi coupling with **9**, a template developed and used effectively in the past by Negishi's group[7] for selective monocouplings at the iodide site. We had tried the corresponding iodochloro template **5**, which displays wider general reactivity in a variety of cross-coupling reactions compared with **9**,[5] but the chloride proved to be too unreactive for the next reaction in this sequence. In a separate flask, we set out to hydrometalate 1-octyne (**11**) and initially tried hydroboration as we have used in the past.[3,5] We envisioned that we could use a base like CsF that would allow us to use anhydrous reaction conditions to set up a potential one-pot Suzuki/Sonogashira[8] coupling sequence. However, boronic acids display a strong tendency to dimerize, and this was the case with the *trans* 1-octenyl boronic acid intermediate derived from **11**. Next we tried to generate the corresponding organozinc reagent to attempt sequential Negishi couplings[7] by first hydrozirconating **11** with Schwartz reagent[9] and transmetallating it to zinc.

(4) For an example of the use of olefin templates to prepare olefin intermediates that were elaborated into ethanolamines via a "libraries from libraries" strategy, see: Organ, M. G.; Kaldor, S. W.; Dixon, C.; Parks, D. J.; Singh, U.; Lavorato, D. J.; Isbester, P. K.; Siegel, M. G. *Tetrahedron Lett.* **2000**, *41*, 8407−8411.

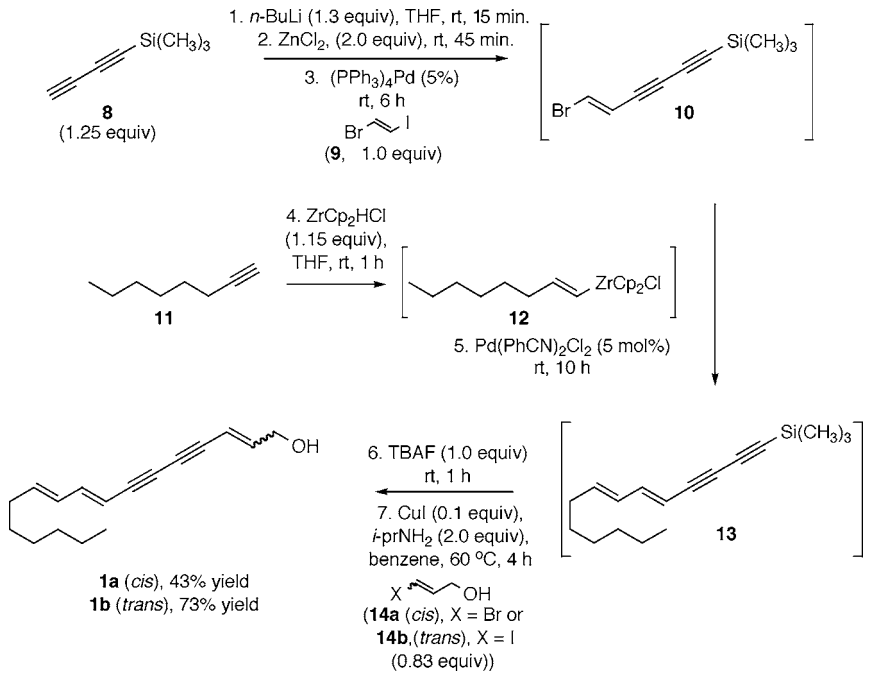
(5) (a) Organ, M. G.; Antunes, L. M. *Tetrahedron Lett.* **2003**, *44*, 6805−6808. (b) A similar approach was used by us recently to prepare (13*E*,15*E*,18*Z*,20*Z*)-1-hydroxypentacosa-13,15,18,20-tetraen-11-yn-4-one 1-acetate; see: Organ, M. G.; Ghasemi, H. *J. Org. Chem.* **2004**, *69*, 695−700.

(6) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(7) Zeng, F.; Negishi, E.-i. *Org. Lett.* **2001**, *3*, 719−722.

(8) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 521−549.

Scheme 1



Despite several attempts, we were never able to isolate the product of cross-coupling from this intermediate, and the reason for this remains unclear. However, we were delighted to find out that the zirconium intermediate itself was a highly reactive coupling partner, thus eliminating the metal/metal exchange step. The contents of the flask containing **12** were added to the first flask containing ene diyne **10**, and this led to the smooth formation of intermediate **13**. With some experimentation we found that this coupling was further enhanced by the concurrent addition of $Pd(PhCN)_2Cl_2$. Removal of the TMS group in situ with TBAF provided the penultimate compound that would serve as the substrate for the Sonogashira coupling with **14a**. This final transformation completed this two-flask, continuous sequence of queued metal-catalyzed reactions providing *cis*-bupleuynol (**1a**) in 43% yield.[10,11] The entire process including chromatography was completed in less than 1 day, and the overall yield saw a 7-fold increase over our previously reported approach.[5a]

To demonstrate the modularity of this olefin template strategy using catalysis, the corresponding *trans*-bupleurynol (**1b**) was prepared using the exact same protocol with the exception that *trans*-3-iodo-2-propen-1-ol (**14b**) was used in the last step, providing the product now in an even higher 73% yield.[12] The improved yield is most likely attributable to the more reactive iodide in the oxidative addition step and the fact that the *trans* halide is much more sterically accessible.

In summary, we have demonstrated that Pd-catalyzed reactions can be used very effectively in queued coupling reactions to convert multiply functionalized olefin building blocks into their corresponding targets. Specifically, four known, commercially available simple building blocks have been converted into relatively complex, conjugated ene diyne targets **1a** and **1b**. In doing so, an already effec-

(9) (a) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679−680. For a review, see: (b) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853−12910.

(10) **(2*Z*,8*E*,10*E*)-Heptadeca-2,8,10-triene-4,6-diyn-1-ol (1a).** All of the following procedures were conducted in flame-dried flasks under argon. To a suspension of 390 mg of $HZrCp_2Cl$ (1.15 equiv, 1.51 mmol) in 2 mL of THF was added 140 mg of 1-octyne (**11**, 1.0 equiv, 1.31 mmol), and the reaction mixture was stirred at room temperature for 1 h. In a second flask, a solution of 200 mg of **8** (1.25 equiv, 1.64 mmol) in 1 mL of THF was treated with *n*-butyllithium (1.31 equiv, 1.72 mmol, 1.2 mL of a 1.4 M solution in pentane) at −78 °C. The reaction mixture was warmed to room temperature and stirred for 15 min, after which 5.3 mL of a 0.5 M $ZnCl_2$ solution in THF (2.0 equiv, 2.62 mmol) was added. After 45 min, 310 mg of (*E*)-1-bromo-2-iodo ethene (**9**, 1.0 equiv, 1.31 mmol) and 80.0 mg of $(PPh_3)_4Pd$ (0.05 equiv, 0.07 mmol) were added, and the mixture was further stirred at room temperature for 6 h. After the reaction was judged complete by proton NMR spectroscopy, it was transferred by cannula to the first flask followed by 25.0 mg of $Pd(PhCN)_2Cl_2$ (0.05 equiv, 0.07 mmol). The reaction mixture stirred at room temperature for 10 h at which time the formation of **13** was judged complete by proton NMR spectroscopy. TBAF (1.0 equiv, 1.31 mmol, 1.31 mL of a 1 M solution in THF) was added, and the mixture was stirred at room temperature for 1 h. In a separate flask, a solution was prepared consisting of 200 mg of **14a** (0.83 equiv, 1.10 mmol), 80.0 mg of $(PPh_3)_4Pd$ (0.05 equiv, 0.07 mmol), 25.0 mg of CuI (0.1 equiv, 0.13 mmol), and 270 mg of $^iPr_2NH$ (2.0 equiv, 2.62 mmol) in 5 mL of benzene. This was added to the reaction, and the mixture was further stirred at 60 °C for 4 h. When the reaction was judged complete by proton NMR spectroscopy, it was run through a short pad of silica gel and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (R_f = 0.3; 30% ethyl acetate in hexane) to provide 0.11 g (43% yield) of the product as an amorphous orange solid. ^1H NMR ($CDCl_3$): δ 6.71 (dd, J = 15.6, 10.8 Hz, 1H), 6.23 (dt, J = 11.2, 5.9 Hz, 1H), 6.11 (dd, J = 14.8, 11.2 Hz, 1H), 5.89 (m, 1H), 5.67 (d, J = 11.2 Hz, 1H), 5.56 (d, J = 15.6 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H), 2.12 (m, 2H), 1.38 (m, 2H), 1.28 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 145.72 (−), 144.95 (−), 140.57 (−), 129.47 (−), 109.67 (−), 107.10 (−), 83.10 (+), 79.92 (+), 77.65 (+), 75.15 (+), 61.20 (+), 32.91 (+), 31.67 (+), 28.88 (+), 28.86 (+), 22.58 (+), 14.07 (−). IR (neat): 3337, 2195, 1634, 1457 cm^{-1}. HRMS (CI): *m*/*z* calcd for $C_{17}H_{22}O$ 242.1671, found 242.1657. Spectra compared identically with that reported for the compound from its isolation (see ref 11).

tive 9-step synthesis of **1a** was compressed into a single synthetic operation. Importantly, no protecting group chemistry was required in this approach, further punctuating the high level of efficiency that can be obtained using late transition metal catalysis. The TMS group on **8** was only necessary to make the compound a liquid and therefore more convenient to handle. We are presently designing and preparing other templates and using them in additional total synthesis projects that will be reported in due course.

Acknowledgment. Financial support for this research came from NSERC (Canada), the Ontario Research and Development Challenge Fund (Ontario), and MDS SCIEX Inc..

Supporting Information Available: Carbon NMR spectra for compounds **1a** and **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) **(2*E*,8*E*,10*E*)-Heptadeca-2,8,10-triene-4,6-diyn-1-ol (1b).** The same procedure described in footnote 10 was used with the exception that template **14b** was used in place of **14a**. The product was obtained in 73% yield as an orange powder. ^{1}H NMR ($CDCl_3$): δ 6.70 (dd, J = 15.6, 10.8 Hz, 1H), 6.39 (dt, J = 16.0, 4.8 Hz, 1H), 6.11 (m, 1H), 5.88 (m, 2H), 5.55 (d, J = 15.2 Hz, 1H), 4.26 (d, J = 4.8 Hz, 2H), 2.12 (m, 2H), 1.40 (m, 2H), 1.28 (m, 6H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 145.50 (−), 144.87 (−), 140.32 (−), 129.50 (−), 109.29 (−), 107.26 (−), 81.59 (+), 80.14 (+), 75.49 (+), 74.95 (+), 62.83 (+), 32.90 (+), 31.67 (+), 28.90 (+), 28.87 (+), 22.58 (+), 14.07 (−). IR (neat): 3372, 2201, 1634, 1586 cm^{-1}. HRMS: calcd for $C_{17}H_{22}O$ 242.1671, found 242.1668. Spectra compared identically with that reported for the compound from its isolation (See ref 11).