ORGANIC LETTERS

2009
Vol. 11, No. 13
2722−2723

Functional Group Compatibility. Propargyl Alcohol Reduction in the Presence of a Vinyl Iodide

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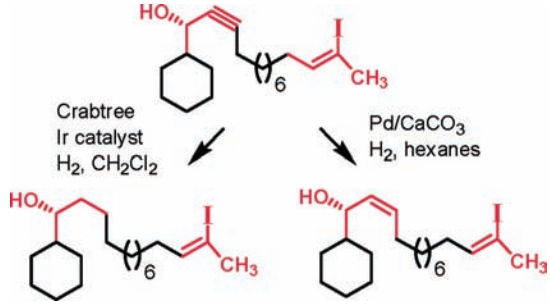
Received April 28, 2009

ABSTRACT



Vinyl iodides are stable to the reduction of propargyl alcohols to cis allylic alcohols by hydrogen over $Pd/CaCO_3$ in hexane. They are also stable to the reduction of propargyl alcohols to saturated alcohols by hydrogen over Crabtree's iridium catalyst in CH_2Cl_2.

Our interest in designing and implementing optimally convergent schemes for the synthesis of polyketide antibiotics led us to consider the possibility of directly reducing the alkyne bond of a propargyl alcohol system to a cis olefin in the presence of a vinyl iodide. Vinyl iodides are generally believed to be incompatible with conditions that would reduce an alkyne to an olefin or to a saturated carbon−carbon bond.[1]

The particular system of interest to us was the conversion of propargyl alcohol **3** to cis allylic alcohol **2**, an advanced intermediate in a projected short synthesis of discodermolide **1** (Scheme 1).[2] Olefin **2** would need only a protection step before linkage to a stereopentad-containing synthon, a key step that would complete the construction of the carbon skeleton of the target. The ability of the vinyl iodide to withstand the reduction conditions was essential to the optimal convergence of the synthesis.

In order to test conditions that might effect the key transformation, we needed a model system for which the substrate and product would be nonvolatile and easily handled. Furthermore, we desired a model substrate that could be prepared easily from commercially available materials by a short sequence. We believed that the substrate requirements would be met by propargyl alcohol **9** (Scheme 2), which we considered the addition product of alkyne **7** and cyclohexanecarboxaldehyde (**8**). Iodoolefinic alkyne **7** might be conveniently prepared from the inexpensive 10-undecenal (**4**). Therefore, we converted aldehyde **4** to the iodo olefin **5** and then cleaved the unsubstituted terminal double bond with OsO_4 followed by $NaIO_4$ to obtain aldehyde **6**. Treatment of this compound with the Ohira−Bestmann reagent[3] afforded alkyne **7**. Addition of the

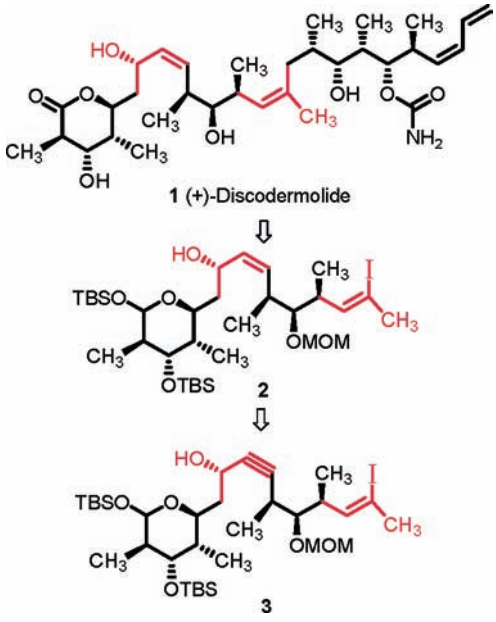
(1) (a) de Lemos, E.; Poree, F.-H.; Bourin, A.; Barbion, J.; Agouridas, E.; Lannou, M.-I.; Commercon, A.; Betzer, J.-F.; Pancrazi, A.; Ardisson, J. *Chem.—Eur. J.* **2008**, *14*, 11092. (b) Arefolov, A.; Panek, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 5596. (c) Arefolov, A.; Panek, J S. *Org. Lett.* **2002**, *4*, 2397.

(2) For related work, see: (a) Cao, H.; Parker, K. A. *Org. Lett.* **2008**, *10*, 1353. (b) Xie, Q.; Denton, R. W.; Parker, K. A. *Org. Lett.* **2008**, *10*, 5345. (c) Parker, K. A.; Wang, P. *Org. Lett.* **2007**, *9*, 4793.

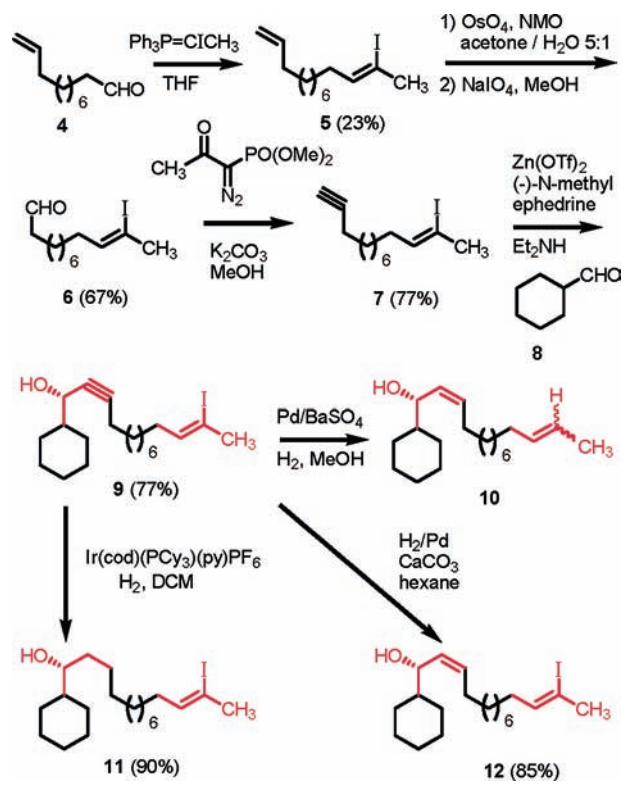
(3) Roth, G. J.; Liepold, B.; Muller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59; Corrigendum: *Synthesis* **2004**, 640.

10.1021/ol900927a CCC: $40.75
Published on Web 05/28/2009

Scheme 1



Scheme 2



corresponding Carreira reagent[4] to aldehyde **8** afforded substrate **9** for our feasibility studies.

We then proceeded to survey reaction conditions. Treatment of alcohol **9** with 1 atm of hydrogen gas in the presence of commercially obtained "Lindlar catalyst" (Fluka)[5] resulted in the recovery of starting material. Likewise, application of the recently introduced method of Wu [$Pd(OAc)_2$, Ph_3P, methoxide in methanol][6] returned alcohol **9**. Treatment of substrate **9** with hydrogen in the presence of 5% $Pd/BaSO_4$ resulted in the recovery of allylic alcohol **10** in which the iodo olefin had also been reduced. More interesting was the reaction in methylene chloride in the presence of Crabtree's iridium catalyst [$Ir(cod)(PCy_3)(py)PF_6$].[7] This gave 90% of alcohol **11** in which the vinyl iodide was still intact but the alkyne bond had been completely reduced to the saturated system. Although the survival of the vinyl iodide during reduction of alkynol to alkanol was not our goal in this study, we suspect that this protocol will find applications in schemes directed toward other targets.

Some of the desired alcohol **12** was obtained by treatment of substrate **10** with diimide. However, the reaction was difficult to control, and conversion was always less than 50%. Hydrogenation over $Pd/CaCO_3$ in methanol gave a mixture of the desired **12** and over-reduced alcohol **10** (ratio $\approx$ 1/6). However, modification of the catalyst system by the substitution of hexanes for methanol as solvent led to encouraging mixtures of starting material and alcohol **12**. Optimization of these conditions provided the target alcohol **12** in 86% yield.

The selective reductions described herein, (**9** → **11**) and (**9** → **12**), offer the chemist new latitude in the design of schemes for the synthesis of complex molecules. The pursuit of some of these opportunities is underway in our laboratory.

Acknowledgment. This work was supported by the Army Breast Cancer Initiative (BC 051816), the National Institutes of Health (GM 74776), and the National Science Foundation (CHE-0131146, NMR instrumentation).

Supporting Information Available: Detailed descriptions of the experimental procedures and complete analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900927A

(4) Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813.

(5) Approximately 5% $Pd/CaCO_3$, poisoned with lead.

(6) Wei, L.-L.; Wei, L.-M.; Pan, W.-B.; Leou, S.-P.; Wu, M.-J. *Tetrahedron Lett.* **2003**, *44*, 1979.

(7) (a) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655. (b) Crabtree, R. H.; Felkin, H.; Fillebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183.