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# On the use of deuterium isotope effects in chemical synthesis

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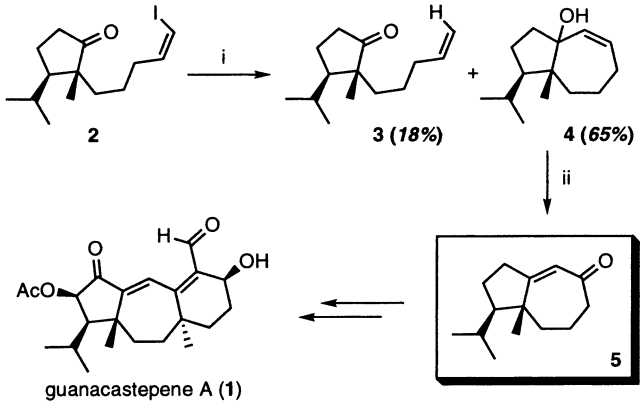
**Abstract**—The decreased kinetic acidity of deuterium relative to hydrogen can be used to gain an advantage in the reductive cyclization of an alkenyllithium species onto a ketone. The intermediate alkenyllithium can add to the carbonyl or abstract an α-proton, giving rise to two products. The yield of the cyclized product can be increased, and the formation of the uncyclized by-product can be suppressed, by replacing the acidic protons with deuterons prior to cyclization. 

During the course of our recently completed total synthesis[1] of guanacastepene A,[2,3] we prepared hydroazulene **5** via a cycloheptenone annulation strategy,[4] as depicted in Scheme 1.

Although the cyclization reaction provided ready access to gram quantities of **5**, the formation of the uncyclized by-product (**3**) clearly detracted from its quality. In this Letter we describe a method that indeed resulted in a sharp improvement in the ratio of productive reductive cyclization to non-productive reduction (see formation of **4** and **3**).

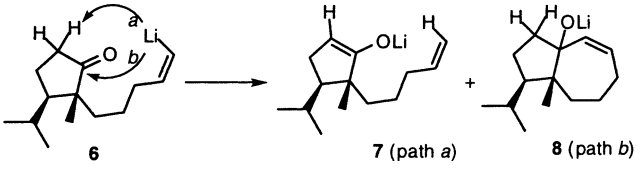



**Scheme 1.** (i) 5.0 equiv. *n*-BuLi (inverse addition), 0°C, THF, 30 min; (ii) PCC, powdered sieves, $CH_2Cl_2$, 70–92% (**4** to **5**).

In charting our course, we surmised that the alkenyllithium species (**6**, Scheme 2), which is derived from **2** by facile lithium–iodine exchange with *n*-butyllithium, reacts along divergent pathways to produce intermediates **7** and **8** (the precursors to **3** and **4**, respectively). In path a, protium transfer from the α-carbon[5] gives rise to the uncyclized enolate **7**.[6] By contrast, addition to the carbonyl group (path b) generates the desired tertiary alkoxide **8**.

If this assumption is correct, suppression of the competing proton transfer reaction (**6**→**7**, path a) should correspondingly increase the ratio of **8**:**7** and thence **4**:**3**. We demonstrate that recourse to α-deuterated ketone substantially minimizes the problem of the competing pathway leading to enolate **7**.[7]

Deuteration of ketone **2** was accomplished in two stages (Scheme 3). Initial treatment of **2** with triethylamine in $CD_3OD$ resulted in the exchange of only one hydrogen atom. Interestingly, this mono-deuteration was stereoselective, indicating a greater kinetic lability of the α-disposed hydrogen towards the weak base.[8] Deuterium incorporation was essentially complete within 3 h; no further change was noted after 20 h at rt.




**Scheme 2.** Proposed competing reaction pathways.[5]

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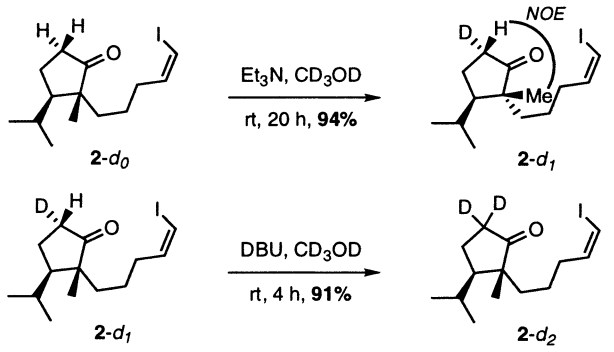


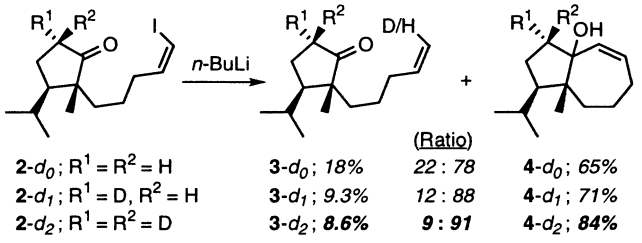

**Scheme 3.** Deuterium incorporation.

However, the stronger base DBU effectively mediated the formation of **2**-$d_2$.

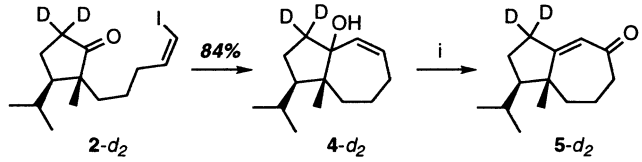
The cyclization reactions of **2** were carried out using the procedure reported previously,[1a] and the two products (**3** and **4**) were isolated following chromatographic purification on silica gel (Scheme 4).[9]

Although the incorporation of deuterium did not completely prevent the formation of non-cyclized reduction products **3**, it did impact the product distribution between **3** and **4** in the desired sense.[10] While recourse to deuterium isotopes is a well-established modus operandi in mechanistic studies, the use of such effects to gain an advantage in preparative synthesis is perhaps an underutilized tactical option.[7] Of course, the case at hand is particularly favorable because the isotope is easily introduced and would be readily removed en route to **1** (Scheme 5).

In summary, the decreased kinetic acidity of deuterium enabled a key cyclization reaction to be accomplished with less contamination from an unwanted by-product. This effect should be broadly applicable in cases where proton transfer reactions compete with the desired reaction pathway.




**Scheme 4.** Effect of deuterium incorporation on the yield and product distribution of the reductive cyclization reaction.




**Scheme 5.** (i) PCC, powdered sieves, $CH_2Cl_2$, ca. 80%.

## Acknowledgements

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4. Piers, E.; Walker, S. D.; Armbrust, R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 635–637.
5. Proton transfer may occur either inter- or intramolecular fashions.
6. The intercession of enolate **7** in the pathway culminating in **3** was supported by isolation of the corresponding enol acetate following quenching with acetic anhydride (Ref. 1a).
7. For a general discussion of isotope effects, see: Lowry, T. H.; Richardson, K. S. Isotope effects. In *Mechanism and Theory in Organic Chemistry*, 3rd ed.; HarperCollins: New York, 1987; pp. 232–244. For related applications to synthesis, see: (a) Laplaza, C. E.; Davis, W. M.; Cummins, C. C. *Organometallics* **1995**, *14*, 577–580; (b) Schrock, R. R.; Baumann, R.; Reid, S. M.; Goodman, J. T.; Stumpf, R.; Davis, W. M. *Organometallics* **1999**, *18*, 3649–3670; (c) Vedejs, E.; Little, J. *J. Am. Chem. Soc.* **2002**, *124*, 748–749.
8. Assigned based on NMR analysis: $^1H$, $^{13}C$, COSY, HMQC, and NOESY. A key NOE interaction is shown in Scheme 3.
9. Some erosion of deuterium labeling was observed in **3**-$d_1$ and **3**-$d_2$, indicating that perhaps iodobutane or adventitious moisture is also involved in the protonolysis of alkenyllithium **6**. This erosion makes it difficult to precisely quantify the observed deuterium effect.
10. The failure to abrogate the non-productive reduction reaction may in part be due to competing hydrogen transfer from solvent or during the metallation event.