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Application of the 2-Azaallyl Anion Cycloaddition Method to Syntheses of (±)-Crinine and (±)-6-Epicrinine

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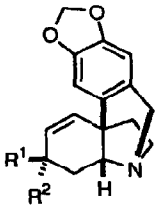
Abstract: Transmetalation of the (2-azaallyl)stannane **9** with *n*-BuLi produced the 2-azaallyl anion **12** which underwent an intramolecular cycloaddition with an alkene to give the perhydroindole **10** in 80% yield as a single stereoisomer. Transformation of **10** to 6-epicrinine **2** and crinine **1** was readily accomplished.

The *Amaryllidaceae* alkaloids continue to be of interest as synthetic targets due to the wide range of biological activities exhibited by these bases.[1] We wish to report a total synthesis of the *Amaryllidaceae* alkaloid crinine **1**[1-3] in 8 steps and 20% overall yield from the known alkyne **3**. 6-Epicrinine **2**[4] is an intermediate in the synthesis of crinine.

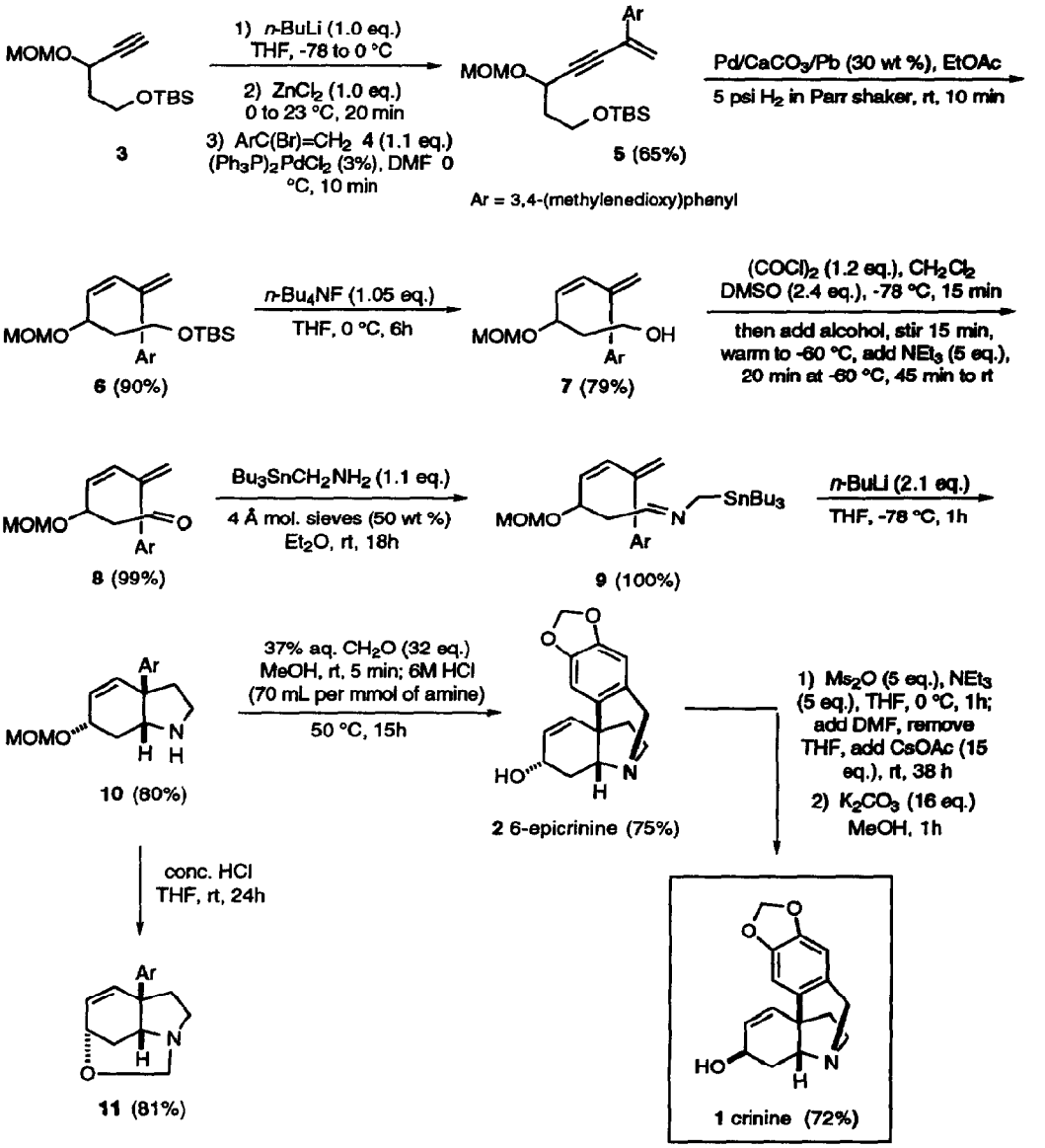


R^1 = OH, R^2 = H: Crinine **1**
R^1 = H, R^2 = OH: 6-Epicrinine **2**

Reports from our laboratories have demonstrated that monocyclic and fused-bicyclic pyrrolidines may be synthesized by inter- and intramolecular [π4s + π2s] cycloadditions of nonstabilized 2-azaallyl anions with electron-rich alkenes.[5] The anions are generated by tin-lithium exchange of (2-azaallyl)stannanes. As an extension of this work, we have begun to apply this method to the synthesis of various pyrrolidine-containing alkaloids.[6]

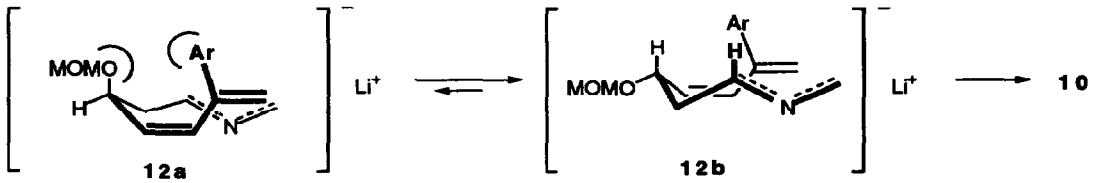
The starting material for our crinine synthesis is the known[6] protected propargyl alcohol **3**, which was prepared by the addition of lithium acetylide-TMEDA complex to 3-(*t*-butyldimethylsilyl)oxypropanal followed by protection of the resultant alcohol (MOMCl, Hünig's base). Formation of the zinc acetylide of **3** followed by palladium-catalyzed coupling with the known vinyl bromide **4**[2c,7] using a modification of King and Negishi's method[8] gave the enyne **5**. The use of DMF as solvent in the palladium coupling was found to be superior to THF. The enyne **5** is a sensitive compound which must be used immediately after purification by radial chromatography (SiO_2). Lindlar reduction of **5** gave the (Z)-diene **6**. Removal of the silyl protecting group gave **7**, which was oxidized to the aldehyde **8** using Swern's method.[9] Condensation of **8** with (aminomethyl)tri-*n*-butylstannane[5c] provided the (2-azaallyl)stannane **9** in quantitative yield. Without

purification, **9** was added to *n*-BuLi in THF at -78 °C. Aqueous workup produced the cycloadduct **10** as a single diastereomer in 80% yield. The facility of this cycloaddition process illustrates the potential power of the 2-azaallyl anion method for the synthesis of relatively complex pyrrolidine-containing targets.



Scheme. Synthesis of (±)-Crinine **1** and (±)-6-Epicrinine **2**

The stereochemical assignment of **10** was supported by the easy formation of the cyclic aminal **11** upon treatment with aqueous acid. Hence, the cycloaddition of the anion derived from **9** had provided the *trans* relationship between the allylic oxygen and the ring juncture substituents rather than the *cis* relationship as required for crinine. Fortunately, the stereochemistry can be adjusted easily (vide infra). Examination of molecular models shows that the (Z)-double bond of the diene exerts a strong influence on the reactive conformation of the 2-azaallyl anion. Two conformations leading to the *cis* ring juncture are shown below (**12a** and **12b**). In conformation **12a**, which would lead directly to the crinine stereochemistry, a serious steric interaction between the allylic methoxymethoxy group and the aromatic ring is evident. A rationale for the predominance of the *cis* ring juncture over the *trans* is not readily apparent from the examination of models, but this observation is consistent with our previous work.[5a,b,6,10]



Completion of the synthesis required the inversion of the allylic stereocenter and a Pictet-Spengler reaction. Although inversion of the allylic alcohol which would be derived from the deprotection of **10** is has close literature precedent,[2f] we found that a step could be saved by subjecting **10** directly to Pictet-Spengler conditions. Thus, deprotection of the methoxymethoxy group and aminomethylation of the arene occured in one operation to give (±)-6-epicrinine **2** in good yield, mp 234-235 °C (lit.[4] mp 235-239 °C). Using the conditions developed by Martin,[2f] the allylic alcohol of **2** was converted to the mesylate and inverted with cesium acetate. Without workup or isolation, saponification of the acetate was carried out by addition of potassium carbonate and methanol to give (±)-crinine **1** in 72% yield, mp 175-177 °C (lit.[2f] mp 172.5-174 °C), which had spectral data in accord with published values.[2f]

The 2-azaallyl anion method has thus proven its utility for the assembly relatively complex alkaloids by allowing the assembly of (±)-crinine in only 8 steps in 20% overall yield. The high efficiency and stereoselectivity of the cycloaddition are particularly promising. Further applications of this methodology to alkaloids synthesis are underway and will be published in due course.

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REFERENCES AND NOTES

(1) Martin, S. F. In *The Alkaloids*; A. Brossi, Ed.; Academic Press, Inc.: New York, 1987; Vol. 30; pp 251-376.

(2) Previous syntheses of crinine: (a) Muxfeldt, H.; Schneider, R. S.; Mooberry, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3670. (b) Whitlock, H. W., Jr.; Smith, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 3600-3606. (c) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629-6637. (d)

Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745-9. (e) Martin, S. F.; Campbell, C. L. *Tetrahedron Lett.* **1987**, *28*, 503-506. (f) Martin, S. F.; Campbell, C. L. *J. Org. Chem* **1988**, *53*, 3184-3190.

(3) For references to synthetic efforts on alkaloids related to crinine, see ref. 2f above.

(4) Synthesis of 6-epicrinine: Kametani, T.; Kohno, T.; Charubala, R. *Chem. Pharm. Bull.* **1972**, *20*, 1488-1490.

(5) (a) Pearson, W. H.; Szura, D. P.; Harter, W. G. *Tetrahedron Lett* **1988**, *29*, 761-764. (b) Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329-1345. (c) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1992**, *57*, 6354-6357. (d) Pearson, W. H.; Stevens, E. P. *Tetrahedron Lett.* **1994**, *35*, 2641-2644.

(6) For an approach to 6a-epipretazettine and 6a-epiprecriwelline, see: Pearson, W. H.; Postich, M. J. *J. Org. Chem* **1994**, *59*, 0000 (in press).

(7) See also: Newman, M.; Dhawan, B.; Hahem, M.; Khanna, B. K.; Springer, J. M. *J. Org. Chem.* **1976**, *41*, 395.

(8) King, A. O.; Negishi, E. *J. Org. Chem* **1978**, *43*, 358-360.

(9) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem* **1978**, *43*, 2480-2482.

(10) Pearson, W. H.; Walters, M. A.; Oswell, K. D. *J. Am. Chem. Soc.* **1986**, *108*, 2769-2771.

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