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 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. We wish to report a total synthesis of the Amaryllidaceae alkaloid crinine 1 in 8 steps and 20% overall yield from the known alkyne 3. 6-Epicrinine 2 is an intermediate in the synthesis of crinine.

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. 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.

The starting material for our crinine synthesis is the known6 protected propargyl alcohol 3, which was prepared by the addition of lithium acetylide-TMEDA complex to 3-(t-butyldimethylsilyl)oxypropansl followed by protection of the resultant alcohol (MOMCl, Hüning's base). Formation of the zinc acetylide of 3 followed by palladium-catalyzed coupling with the known vinyl bromide 4 using a modification of King and Negishi's method8 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 (SiO2). 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. Condensation of 8 with (aminomethyl)tri-n-butylstannane5c 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.
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 \textit{trans} relationship between the allylic oxygen and the ring juncture substituents rather than the \textit{cis} relationship as required for crinine. Fortunately, the stereochemistry can be adjusted easily (\textit{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 \textit{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 \textit{cis} ring juncture over the \textit{trans} is not readily apparent from the examination of models, but this observation is consistent with our previous work.\textsuperscript{5a,b,6,10}

\begin{center}
\begin{tikzpicture}
  \node at (0,0) (a) {\includegraphics[width=0.8\textwidth]{12a}};
  \node at (2,0) (b) {\includegraphics[width=0.8\textwidth]{12b}};
  \node at (1,0) {Li\textsuperscript{+}};
\end{tikzpicture}
\end{center}

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,\textsuperscript{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 occurred in one operation to give (±)-6-epicrinine 2 in good yield, mp 234-235 °C (lit.\textsuperscript{4} mp 235-239 °C). Using the conditions developed by Martin,\textsuperscript{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.\textsuperscript{2f} mp 172.5-174 °C), which had spectral data in accord with published values.\textsuperscript{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.

\textbf{Acknowledgment} is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

\textbf{REFERENCES AND NOTES}


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


(Received in USA 6 September 1994; accepted 14 October 1994)