

Concise Synthesis of
Anhydrovinblastine from Leurosine

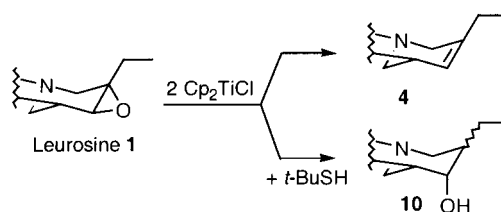
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Received January 15, 2002

ABSTRACT

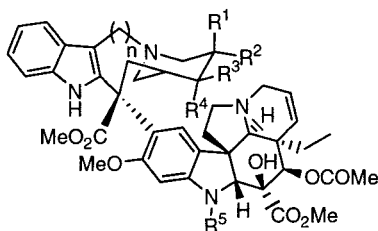


The Cp_2TiCl -mediated deoxygenation of leurosine (**1**) afforded anhydrovinblastine (**4**) in good yield. Furthermore, as the reaction proceeded via a carbon-centered radical intermediate, this transient was also trapped by a hydrogen-atom donor to afford selectively reduced alkaloid **10**.

Leurosine¹ (**1**) is one of the most abundant bisindole alkaloids isolated from the leaves of the Madagascan periwinkle *Catharantus roseus*. It was formerly classified in the family of Vinca alkaloids, which also included vinblastine (**2**), vincristine (**3**), and anhydrovinblastine (**4**) (Scheme 1).² Together with vinorelbine³ (**5**) (Navelbine), a semisynthetic derivative currently on the market, these dimeric alkaloids

inhibit mitosis by binding to tubuline, thus allowing a broad spectrum of activity in the treatment of various carcinomas.^{2,4} The synthesis of Navelbine (**5**) requires two steps: the biomimetic coupling of two monomers (catharanthine (**6**) and vindoline (**7**)) to afford anhydrovinblastine **4**, followed by contraction of the latter's C' ring (Scheme 2).⁵ Anhydrovinblastine is thus the key intermediate in the synthesis of the anticancer drug Navelbine. Herein, we would like to report a one-step procedure for the synthesis of anhydrovinblastine (**4**) starting from the parent alkaloid leurosine (**1**). Since the alkaloids **1** and **4** differ only by the presence of an epoxide on the "northern" portion of leurosine, the selective deoxy-

Scheme 1

Leurosine (**1**): $n=2$, $R_1=\text{Et}$, $R_2\text{--}R_4: -\text{O}-$, $R_3=\text{H}$, $R_5=\text{Me}$ Vinblastine (**2**): $n=2$, $R_1=\text{OH}$, $R_2=\text{Et}$, $R_3=R_4=\text{H}$, $R_5=\text{Me}$ Vincristine (**3**): $n=2$, $R_1=\text{OH}$, $R_2=\text{Et}$, $R_3=R_4=\text{H}$, $R_5=\text{CHO}$ Anhydrovinblastine (**4**): $n=2$, $R_1=\text{Et}$, $R_2\text{--}R_3: (=)$, $R_4=\text{H}$, $R_5=\text{Me}$ Vinorelbine (**5**): $n=1$, $R_1=\text{Et}$, $R_2\text{--}R_3: (=)$, $R_4=\text{H}$, $R_5=\text{Me}$

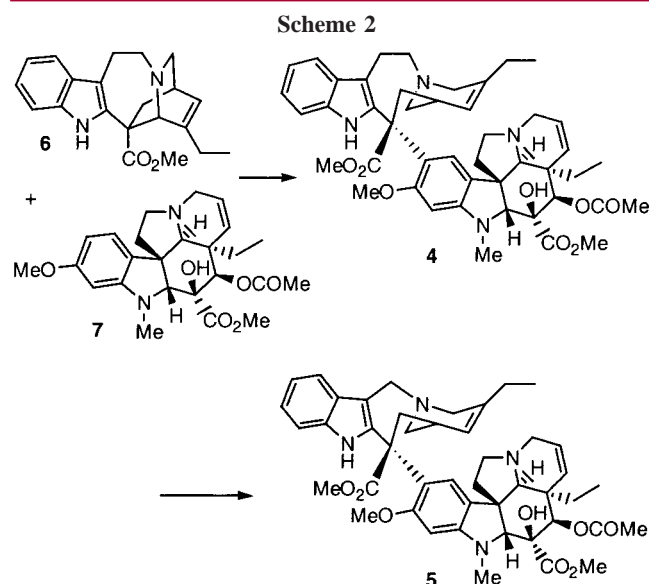
(1) For an X-ray structure of leurosine methiodide, see: Hardouin, C.; Doris, E.; Rousseau, B.; Mioskowski, C.; Nierlich, M. *Acta Crystallogr.* **2000**, C56, 225–226.

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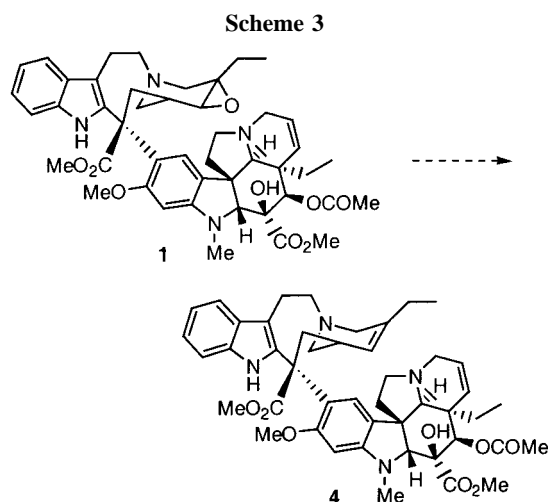
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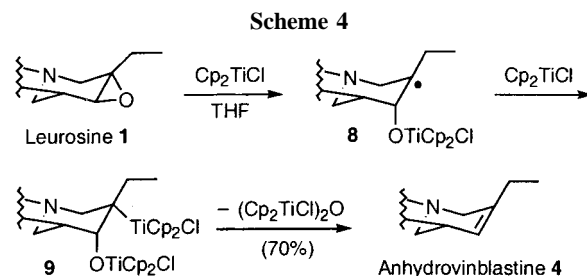
generation of the cyclic ether should thus provide direct access to anhydrovinblastine, as previously demonstrated by Attar-Rahman (Scheme 3).⁶



Our strategy involves the utilization of a low-valent titanium species for the key deoxygenation step. Indeed, Nugent and RajanBabu reported that Cp_2TiCl ⁷ efficiently promotes the conversion of epoxides to the corresponding olefins under mild conditions.⁸ Leurosine (**1**) was therefore reacted with Cp_2TiCl for 15 min at room temperature in THF. The low-valent titanium(III) complex was readily prepared by the in situ reduction of 2.5 equiv of Cp_2TiCl_2 with 5 equiv of powdered zinc for 45 min.⁹ The reaction produced anhydrovinblastine (**4**) cleanly in 70% yield; we identified

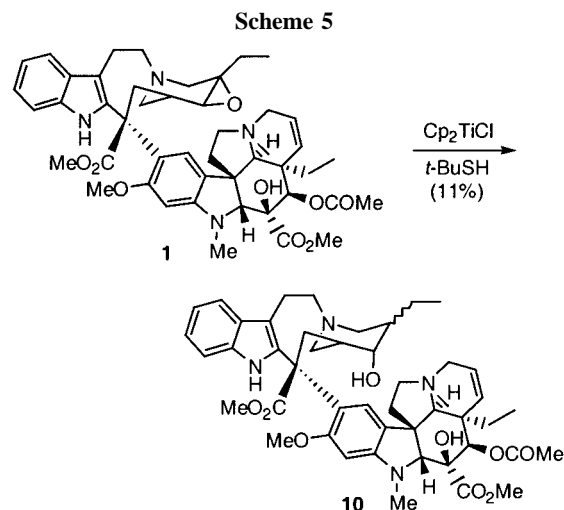
4 unambiguously by spectroscopic and chromatographic comparison with an authentic sample.

A postulated reaction mechanism is illustrated in Scheme 4. In the first step, the sequential single electron transfer from



Cp_2TiCl to the oxirane and homolysis of the C–O bond generate the β -alkoxy radical **8**. The relative stability of the carbon-centered radical intermediate (for example, tertiary > secondary > primary) governs the regiochemistry of the ring opening. Upon reaction with a second equivalent of Cp_2TiCl , the β -alkoxy carbanion **9** results. Subsequent elimination of a titanium-oxo byproduct finally delivers deoxygenated anhydrovinblastine **4**.

The intermediacy of a radical species similar to **8** prompted us to trap this transient by a hydrogen-atom donor.¹⁰ Such radical capture would produce a vinblastine-type alkaloid analogous to **10** by selective reduction of the epoxide (Scheme 5). To corroborate this hypothesis, a THF solution



of Cp_2TiCl was added dropwise to a mixture of leurosine (**1**) and a 10-fold excess of 2-methyl-2-propanethiol. Inverse addition of the titanium reagent to the epoxide was advanta-

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geous to minimize the competing deoxygenation to anhydrovinblastine. This furnished an alkaloid derivative to which we tentatively assign the structure of the bisindole **10**.¹¹ It should be noted that we obtained this product only in modest yield (11%) and as a single diastereomer, albeit with unknown stereochemistry of the ethyl group.

In conclusion, we have shown that the low-valent Cp₂-TiCl efficiently deoxygenates leurosine to anhydrovinblastine.¹² A modified procedure was also applied to the synthesis

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of a vinblastine-type alkaloid by selective reduction of the epoxide moiety of leurosine.

Acknowledgment. This work is part of a collaboration between Pierre Fabre Médicament/CEA-Direction des Sciences du Vivant. Dr. J. Albert Ferreira is gratefully acknowledged for reviewing this manuscript.

Supporting Information Available: Experimental procedures and spectral data for compounds **4** and **10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL025560C