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Concise Synthesis of Anhydrovinblastine from Leurosine

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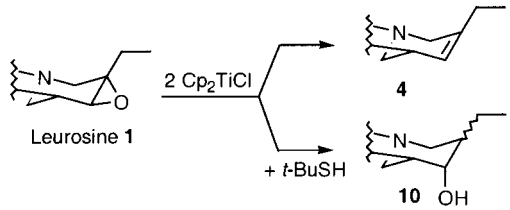
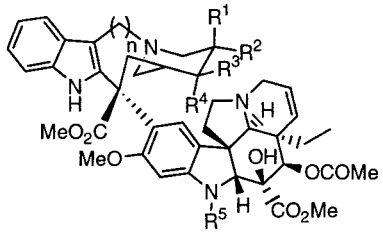
ABSTRACT



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.

Leurosine[1] (**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 vinorelbine[3] (**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= Et, R_2-R_4: -O-, R_3= H, R_5= Me

Vinblastine (**2**): n=2, R_1= OH, R_2= Et, R_3=R_4= H, R_5= Me

Vincristine (**3**): n=2, R_1= OH, R_2= Et, R_3=R_4= H, R_5= CHO

Anhydrovinblastine (**4**): n=2, R_1= Et, R_2-R_3: (=), R_4= H, R_5= Me

Vinorelbine (**5**): n=1, R_1= Et, R_2-R_3: (=), R_4= H, R_5= 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.

(2) The Alkaloids. *Antitumor Bisindole Alkaloids from Catharanthus Roseus (L.)*. Brossi, A., Suffness, M., Eds.; Academic Press: San Diego, 1990; Vol. 37.

(3) Langlois, N.; Guéritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017−7024.

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(5) Mangeney, P.; Andriamialisoa, R. Z.; Lallemand, J. Y.; Langlois, N.; Langlois, Y.; Potier, P. *Tetrahedron* **1979**, *35*, 2175−2179. Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *Tetrahedron* **1980**, *36*, 3053−3060.

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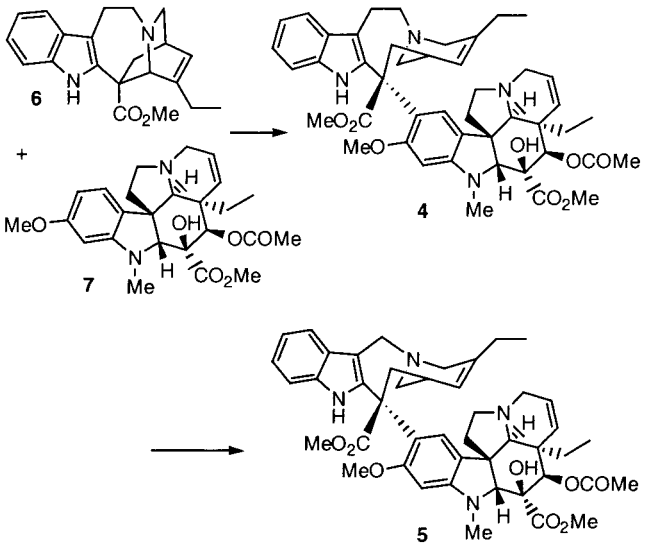
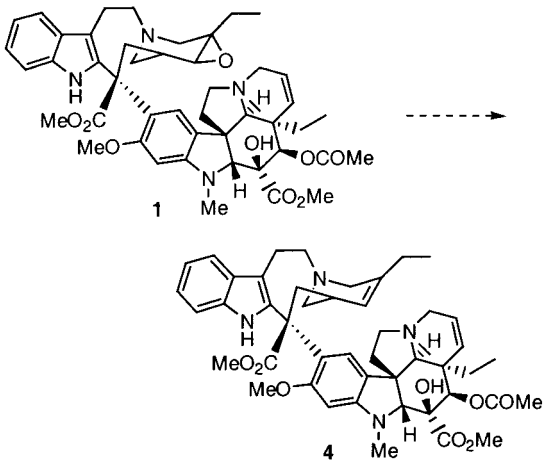
Scheme 2



genation of the cyclic ether should thus provide direct access to anhydrovinblastine, as previously demonstrated by Atta-ur-Rahman (Scheme 3).[6]

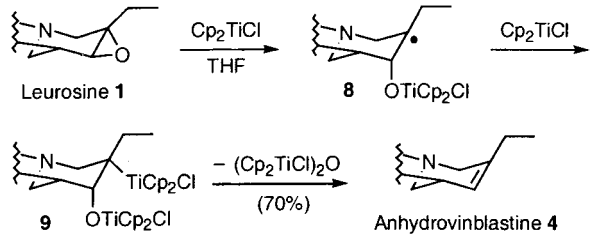
Scheme 3



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

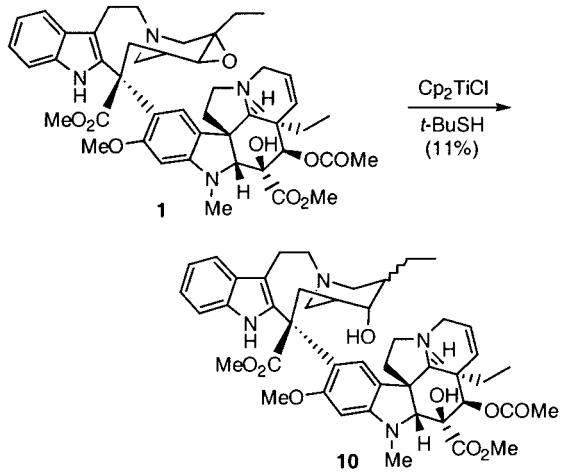
Scheme 4



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

Scheme 5



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-

(6) Atta-ur-Rahman; Perveen, S. *J. Nat. Prod.* **1988**, *51*, 1271−1272.
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(9) Hardouin, C.; Chevallier, F.; Rousseau, B.; Doris, E. *J. Org. Chem.* **2001**, *66*, 1046−1048.

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 Cp_2-TiCl efficiently deoxygenates leurosine to anhydrovinblastine.[12] A modified procedure was also applied to the synthesis of a vinblastine-type alkaloid by selective reduction of the epoxide moiety of leurosine.

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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.

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