JOCNote

Selective Deoxygenation of Leurosine: Concise Access to Anhydrovinblastine

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Abstract: Straightforward access to anhydrovinblastine starting from the parent alkaloid leurosine is reported. The key deoxygenation step was first optimized on a model substrate. However, applied to leurosine, only the low-valent Cp$_2$TiCl gave satisfactory results.

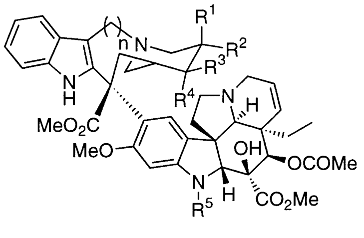
Leurosine **1** is one of the most abundant bisindole alkaloids isolated from the leaves of the Madagascan Periwinkle *Catharanthus roseus*. It was initially classified in the family of *Vinca* alkaloids, which included vinblastine **2**, vincristine **3**, and anhydrovinblastine **4** (Scheme 1).[1]

Together with vinorelbine **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] The synthesis of Navelbine **5** requires two steps: the biomimetic coupling of two monomers (catharanthine **6** and vindoline **7**) to afford anhydrovinblastine **4**[3], followed by contraction of the latter's C′ ring (Scheme 2).[4]

Anhydrovinblastine is thus the key intermediate in the synthesis of the anticancer drug Navelbine. Since the alkaloids **1** and **4** differ only by the presence of an epoxide on the "northern" portion of leurosine, the selective deoxygenation of the cyclic ether should thus provide direct access to anhydrovinblastine as previously demonstrated by Atta-ur-Rahman using TMSCl/Zn dust (Scheme 3).[5]

In the present article we report a detailed account of our investigations for the synthesis of anhydrovinblastine **4** starting from the parent alkaloid leurosine **1**.

SCHEME 1



Leurosine (**1**): n=2, R_1= Et, R_2-R_4: -O-, R_3= H, R_5= Me

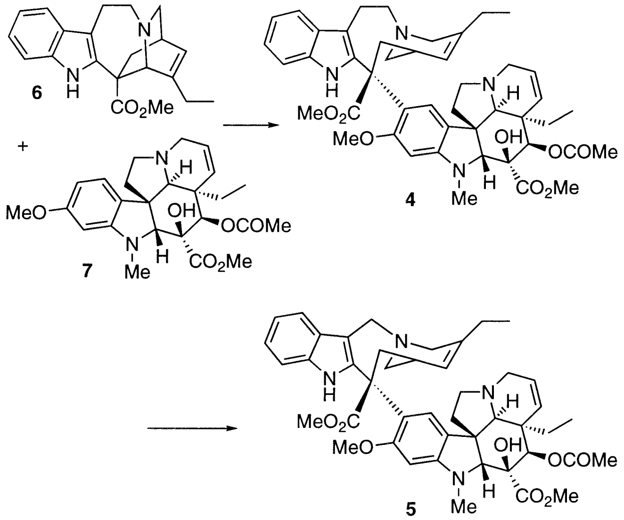
Vinblastine (**2**): n=2, R_1= OH, R_2= Et, R_3=R_4= H, R_5= Me

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

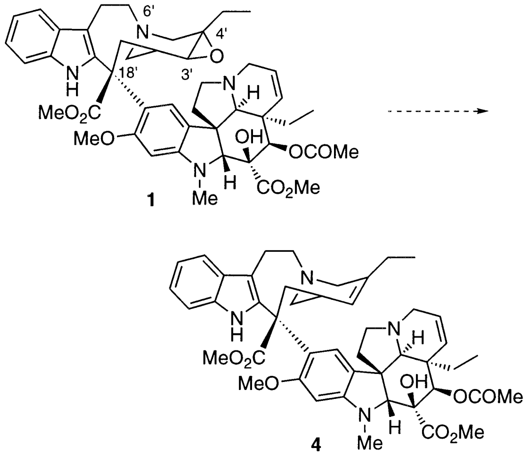
Anhydrovinblastine (**4**): n=2, R_1= Et, R_2-R_3: (=), R_4= H, R_5= Me

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

SCHEME 2



SCHEME 3



The structure of leurosine was established in 1969 by spectroscopic comparison with related alkaloids[6] and

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

(2) Zavala, F.; Guénard, D.; Potier, P. *Experientia* **1978**, *34*, 1497−1499. Guéritte, F.; Pouilhès, A.; Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *Eur. J. Med. Chem.-Chim. Ther.* **1983**, *18*, 419−424. Lobert, S.; Vulevic, B.; Correia, J. J. *Biochemistry* **1996**, *35*, 6806−6814. Lobert, S.; Fahy, J.; Hill, B. T.; Duflos, A.; Etievant, C.; Correia, J. J. *Biochemistry* **2000**, *39*, 12053−12062.

(3) Potier, P.; Langlois, N.; Langlois, Y.; Guéritte, F. *J. Chem. Soc., Chem. Commun.* **1975**, 670−671. Langlois, N.; Guéritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017−7024.

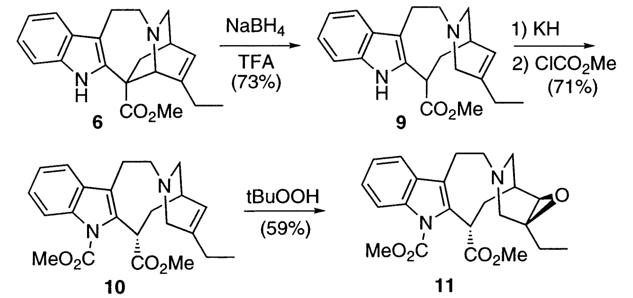
(4) Mangeney, P.; Andriamialisoa, R. Z.; Lallemand, J. Y.; Langlois, N.; Langlois, Y.; Potier, P. *Tetrahedron* **1979**, *35*, 2175−2179. Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *Tetrahedron* **1980**, *36*, 3053−3060.

(5) Atta-ur-Rahman; Perveen, S. *J. Nat. Prod.* **1988**, *51*, 1271−1272.

(6) Abraham, D. J.; Farnsworth, N. R. *J. Pharm. Sci.* **1969**, *58*, 694−698.

10.1021/jo0202942 CCC: $22.00

SCHEME 4

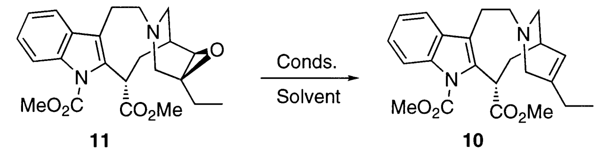


later confirmed by oxidation of anhydrovinblastine.[7] Since no X-ray data were available at this time, we initiated a study to elucidate the solid-state conformation of leurosine. Treatment of leurosine **1** with excess iodomethane furnished leurosine-methiodide **8** (mono-alkylated at N6′). Suitable colorless crystals were obtained by slow evaporation of a MeOH/H_2O/THF solution. The X-ray structure of leurosine-methiodide[8] (see Supporting Information) shows that the central and adjacent six-membered rings of vindoline are in boat and sofa conformations, respectively. The piperidine ring of the upper part of the alkaloid adopts a sofa conformation, while the seven-membered ring incorporating the oxirane is in a boat conformation. The stereochemistry of the epoxide was found to be in agreement with the one previously determined by NMR experiments.[9]

Deoxygenation was first attempted on a model substrate **11**, which incorporates the main structural features of the northern portion of leurosine, including the key epoxide (Scheme 4). Our synthesis of the model substrate started from catharanthine **6**, which was converted to 18-carboxymethoxycleavamine **9** (as a 3/1 mixture of epimers) by a ring-opening/reduction sequence.[10] The indole nitrogen atom was then protected as the methyl carbamate using KH as a base.[11] It should be noted that the center bearing the ester moiety fully epimerized during the basic process. Finally, the oxirane was introduced in 59% yield by *tert*-butyl peroxide epoxidation of the double bond leading to **11**.[12]

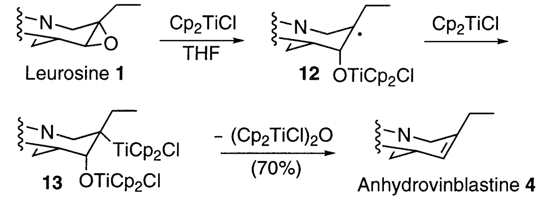
Among the various deoxygenation conditions tested,[13] three procedures gave satisfactory results on the model substrate **11** (Table 1). The utilization of either TMSCl/NaI[14] (entry 1), trifluoroacetic anhydride/NaI[15] (entry 2), or the low-valent Cp_2TiCl[16] (entry 3) permitted the smooth conversion of **11** into deoxygenated derivative **10**.

TABLE 1. Deoxygenation Attempts on Model Substrate 11



entry	conditions	solvent	yield (%)
1	TMSCl/NaI	CH_3CN	81
2	$(CF_3CO)_2O$/NaI	THF/CH_3CN	56
3	Cp_2TiCl_2/Zn	THF	43

SCHEME 5



With these results in hands, we attempted the deoxygenation of leurosine **1** using the aforementioned methods. Unfortunately, the reactions involving NaI combined with either TMSCl or trifluoroacetic anhydride did not allow conversion of **1** into anhydrovinblastine **4**. Leurosine **1** was ultimately treated 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.[17] The reaction produced anhydrovinblastine **4** cleanly in 70% yield. Compound **4** was unambiguously identified by spectroscopic and chromatographic comparison with an authentic sample. Our strategy involving the utilization of a low-valent titanium species for the key deoxygenation step was inspired by the work of Nugent and RajanBabu, who reported that Cp_2TiCl efficiently promotes the conversion of epoxides to the corresponding olefins under mild conditions.[18]

A postulated reaction mechanism is illustrated in Scheme 5. In the first step, the sequential single-electron transfer from Cp_2TiCl to the oxirane and homolysis of the C−O bond generate a β-alkoxy radical **12**. 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, a β-alkoxy carbanion **13** results, followed by subsequent elimination of a titanium-oxo byproduct to provide deoxygenated anhydrovinblastine **4**.

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(7) Langlois, N.; Potier, P. *J. Chem. Soc., Chem. Commun.* **1979**, 582−584.

(8) Hardouin, C.; Doris, E.; Rousseau, B.; Mioskowski, C.; Nierlich, M. *Acta Crystallogr.* **2000**, *C56*, 225−226.

(9) De Bruyn, A.; De Taeye, L.; Simonds, R.; De Pauw, C. *Bull. Soc. Chim. Belg.* **1981**, *90*, 185−189.

(10) Ratremaniaina, Z.; Langlois, N.; Langlois, Y. *Heterocycles* **1981**, *15*, 245−250.

(11) Kutney, J. P.; Balsevich, J.; Bokelman, G. H.; Hibino, T.; Honda, T.; Itoh, I.; Ratcliffe, A. H.; Worth, B. R. *Can. J. Chem.* **1978**, *56*, 62−70.

(12) Kutney, J. P.; Balsevich, J.; Worth, B. R. *Can. J. Chem.* **1979**, *57*, 1682−1690.

(13) For example, see: Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112−127 (NaI/Zn). Suzuki, H.; Fuchita, T.; Iwasa, A.; Mishina, T. *Synthesis* **1978**, 905−908 (P_2I_4/pyridine). Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 251−254 (dimethyl diazomalonate/$Rh_2(OAc)_4$). Paryzek, Z.; Wydra, R. *Tetrahedron Lett.* **1984**, *25*, 2601−2604 (PPh_3I_2). Yamada, K.; Goto, S.; Nagase, H.; Kyotani, Y.; Hirata, Y. *J. Org. Chem.* **1978**, *43*, 2076−2077 (MTPI/$BF_3{\cdot}OEt_2$). Paulsen, H.; Heiker, F. R.; Feldmann, J.; Heyns, K. *Synthesis* **1980**, 636−638 (3-methyl-2-selenoxo-1,3-benzothiazol/CF_3CO_2H).

(14) Caputo, R.; Mangoni, L.; Neri, O.; Palumbo, G. *Tetrahedron Lett.* **1981**, *22*, 3551−3552.

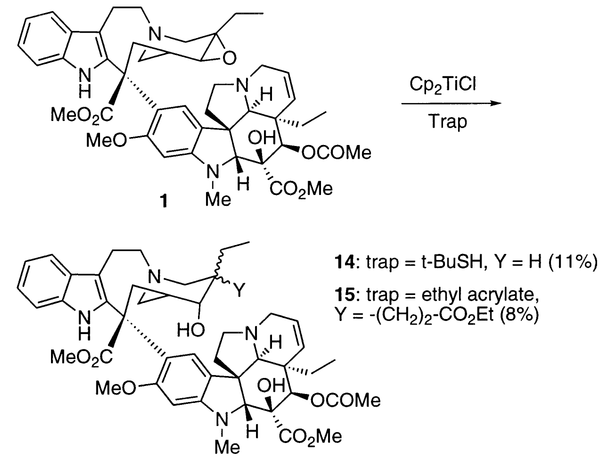
(15) Sonnet, P. E. *J. Org. Chem.* **1978**, *43*, 1841−1842.

(16) Gold, H. J. *Synlett* **1999**, 159. Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771−2788. Li, J. J. *Tetrahedron* **2001**, *57*, 1−24.

(17) Hardouin, C.; Chevallier, F.; Rousseau, B.; Doris, E. *J. Org. Chem.* **2001**, *66*, 1046−1048. Moisan, L.; Hardouin, C.; Rousseau, B.; Doris, E. *Tetrahedron Lett.* **2002**, *43*, 2013−2015. See also ref 18.

(18) RajanBabu, T. V.; Nugent, W. A.; Beattie, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6408−6409. RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986−997. See also: Schobert, R. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 855−856.

SCHEME 6



The intermediacy of a radical species similar to **12** prompted us to trap this transient by either a hydrogen-atom donor[19] or ethyl acrylate.[20] Such radical capture would produce vinblastine-type alkaloids analogous to **14** and **15**, respectively, by selective reduction of the epoxide (Scheme 6). To corroborate this hypothesis, a solution of Cp_2TiCl in THF was added dropwise to a mixture of leurosine **1** and a 10-fold excess of 2-methyl-2-propanethiol. Changing the order of addition of the titanium reagent to the epoxide was required to minimize the competing deoxygenation to anhydrovinblastine. This furnished an alkaloid derivative to which we tentatively assign the structure of the bisindole **14**.[21] 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. The same comments hold true for the synthesis of **15** (8% yield) where ethyl acrylate was used as radical trap instead of *t*-BuSH.

In conclusion, we have shown that the low-valent Cp_2TiCl efficiently deoxygenates leurosine to anhydrovinblastine.[22] This procedure was also applied to the synthesis of vinblastine-type alkaloids (e.g., **14** and **15**) by tandem selective reduction of the epoxide moiety of leurosine/trapping of the resulting radical intermediate.

Experimental Section

General Methods. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz using residual $CHCl_3$ (7.25 ppm) and $CDCl_3$ (77 ppm) as internal standards, respectively. Flash column chromatography was performed on silica gel (60 Å, 230−400 mesh). All reactions were performed under Ar. THF was distilled over Na/benzophenone. HRMS was recorded at the "Centre Régional de Mesures Physiques de l'Ouest" (Rennes, France).

Leurosine-methiodide (8).[8] Leurosine (0.5 g) was added portionwise to 5 mL of CH_3I. The solution was stirred for 1 h at room temperature, and excess CH_3I was removed under reduced pressure. Suitable colorless crystals for X-ray analysis were obtained by slow evaporation of a $MeOH/H_2O$/THF solution.

18-Carboxymethoxycleavamine (9).[10] A solution of catharanthine sulfate (20.16 g, 46.4 mmol, 1 equiv) in 120 mL of CF_3CO_2H was stirred at room temperature for 36 h. $NaBH_4$ (4.5 g, 2.5 equiv) in 40 mL of THF was then cautiously added dropwise, at 0 °C, over a period of 10 min. The reaction mixture was further stirred for 30 min, and the reaction was quenched with saturated $NaHCO_3$. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. After chromatography on silica (5:1 hexane/EtOAc), 18(*S*)- and 18(*R*)-carboxymethoxycleavamine were obtained in a 3:1 ratio (12.9 g, 83% combined yield). 18(*S*)-Carboxymethoxycleavamine (R_f = 0.55 (4:1 hexane/EtOAc), white solid): ^1H NMR ($CDCl_3$) δ 1.07 (t, J = 7.4 Hz, 3H), 2.06 (m, 3H), 2.18 (m, 1H), 2.29−2.41 (m, 4H), 2.72 (m, 1H), 2.86 (m, 2H), 3.12 (m, 2H), 3.66 (s, 3H), 5.17 (d, J = 10 Hz, 1H), 5.29 (d, J = 3.4 Hz, 1H), 7.06−7.17 (m, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 8.59 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.6, 26.3, 27.6, 34.7, 38.2, 38.6, 52.0, 53.1, 53.7, 55.2, 110.5, 111.6, 118.2, 118.9, 121.5, 121.8, 127.9, 134.6, 135.7, 141.5, 175.7; MS (ESI) 338 (M^+, 100); IR (KBr) 3381, 2960, 2921, 1718, 1461, 1159, 741; HRMS calcd for $C_{21}H_{26}N_2O_2$ $(M)^+$ 338.1994, found 338.1987. 18(*R*)-Carboxymethoxycleavamine (R_f = 0.35 (4:1 hexane/EtOAc), white solid): ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.82 (q, J = 7.3 Hz, 2H), 1.91−2.11 (m, 2H), 2.25 (m, 2H), 2.56 (m, 2H), 2.79 (d, J = 15.9 Hz, 1H), 2.91−3.12 (m, 3H), 3.62 (d, J = 12.2 Hz, 1H), 3.76 (s, 3H), 4.08 (dd, J = 2 and 4.9 Hz, 1H), 5.51 (d, J = 4.3 Hz, 1H), 7.09−7.21 (m, 2H), 7.37 (d, J = 7.3 Hz, 1H), 7.58 (d, J = 7.3 Hz, 1H), 9.08 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.2, 21.7, 27.2, 34.1, 39.1, 39.3, 47.0, 51.2, 52.2, 57.5, 109.6, 110.7, 117.6, 118.8, 121.0, 124.2, 128.0, 135.0, 135.2, 138.7, 176.1.

16,18(*S*)-Dicarboxymethoxycleavamine (10).[11] At 0 °C, to a solution of a 3:1 mixture of epimers of 18-carboxymethoxycleavamine (1.4 g, 4.14 mmol, 1 equiv) in 40 mL of THF was added, over a period of 10 min, KH (2 g of a 35% dispersion in oil, 4.2 equiv). The reaction was stirred 30 min at 0 °C, and methyl chloroformate (1.5 mL, 4.9 equiv) was added dropwise at this temperature. The reaction was further stirred for 90 min at room temperature and quenched, at 0 °C, with saturated $NaHCO_3$. The aqueous layer was extracted once with Et_2O and twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. After chromatography on silica (9:1 hexane/EtOAc), 16,18(*S*)-dicarboxymethoxycleavamine was obtained as a pale yellow oil (1.16 g, 71%): ^1H NMR ($CDCl_3$) δ 1.04 (t, J = 7.4 Hz, 3H), 1.90 (m, 1H), 2.02 (q, J = 7.4 Hz, 2H), 2.13 (m, 1H), 2.38 (d, J = 11.6 Hz, 1H), 2.44−2.58 (m, 2H), 2.75−2.86 (m, 4H), 3.06 (s, 2H), 3.58 (s, 3H), 3.94 (s, 3H), 5.41 (d, J = 4.3 Hz, 1H), 5.82 (d, J = 6.7 Hz, 1H), 7.22−7.32 (m, 2H), 7.46 (d, J = 8.2 Hz, 1H), 8.14 (d, J = 9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.6, 26.8, 27.6, 34.7, 35.8, 38.6, 51.8, 52.4, 53.1, 54.3, 54.5, 115.7, 118.1, 119.5, 122.1, 127.7, 124.3, 129.8, 136.0, 137.7, 141.1, 151.9, 173.7; MS (CI/NH_3) 397 ($(M + H)^+$, 100); IR (neat) 2955, 1735, 1459, 1328, 1233, 732.

16,18(*S*)-Dicarboxymethoxy-3(*R*),4(*S*)-epoxydihydrocleavamine (11).[12] To a solution of 16,18(*S*)-dicarboxymethoxycleavamine (1.1 g, 2.77 mmol, 1 equiv) in 60 mL of THF was added a 1% solution of CF_3CO_2H in H_2O (6 mL, 0.3 equiv) and TBHP (5.5 mL of a 70% solution in H_2O, 15 equiv). The reaction mixture was stirred for 24 h at room temperature, and the reaction was quenched with saturated $NaHCO_3$. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with 5% NaOH, H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. After chromatography on silica (4:1 hexane/EtOAc), 16,18(*S*)-dicarboxymethoxy-3(*R*),4(*S*)-epoxydihydrocleavamine was obtained as a pale yellow powder (mp 133 °C, 0.68 g, 59%): ^1H NMR ($CDCl_3$) δ 1.03 (t, J = 7.3 Hz, 3H), 1.47−1.59 (m, 1H), 1.63−1.77 (m, 1H), 2.01−2.16 (m, 3H), 2.40 (m, 1H), 2.59 (m, 1H), 2.71 (m, 1H), 2.79 (m, 2H), 2.95 (m, 3H), 3.11 (d, J = 12.8 Hz, 1H), 3.62 (s, 3H), 3.97 (s, 3H), 5.88 (d, J = 6.7 Hz, 1H), 7.22−7.32 (m, 2H), 7.45 (d, J = 7.3 Hz, 1H), 8.12 (d, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 8.9, 26.2, 29.9, 33.4, 33.5, 39.3, 50.4, 51.9, 52.6, 53.3, 60.6, 62.7, 115.8, 118.1, 119.4, 122.8, 124.4, 129.6,

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[19] Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849−12859. Gansäuer, A. *Synlett* **1998**, 801−809.

[20] RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525−4527.

[21] Compound **14** has already been reported by Kutney et al.; see: Kutney, J. P.; Honda, T.; Kazmaier, P. M.; Lewis, N. J.; Worth, B. R. *Helv. Chim. Acta* **1980**, *63*, 366−374.

[22] Hardouin, C.; Doris, E.; Rousseau, B.; Mioskowski, C. *Org. Lett.* **2002**, *4*, 1151−1153.

135.8, 136.8, 151.9, 173.4; MS (CI/NH$_3$) 413 ((M + H)$^+$, 100); IR (KBr) 2955, 1734, 1461, 1364, 1196, 913, 732; [α]$_D$^{25} + 92 (*c* 0.5, CH$_2$Cl$_2$). HRMS calcd for C$_{23}$H$_{28}$N$_2$O$_5$ (M)$^+$ 412.1998, found 412.1981.

Deoxygenation Attempts on the Model Substrate 11. *Procedure A*.[14] To a suspension of NaI (0.25 g, 10 equiv) in 1 mL of CH$_3$CN was added dropwise TMSCl (0.1 mL, 5 equiv). The yellowish solution was stirred 10 min at room temperature, and a solution of **11** (0.06 g, 0.15 mmol, 1 equiv) in CH$_3$CN was added dropwise. After 1 h, the reaction was quenched with a 2.5 N solution of Na$_2$S$_2$O$_3$ (10 mL). The aqueous phase was extracted three times with Et$_2$O. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. After chromatography on silica (4:1 hexane/EtOAc), **10** was obtained in 81% yield (0.046 g). *Procedure B*.[15] At 0 °C, to a suspension of NaI (0.2 g, 11 equiv) in 2 mL of CH$_3$CN was added dropwise (CF$_3$CO)$_2$O (0.1 mL, 6 equiv). After 5 min, a solution of **11** (0.05 g, 0.12 mmol, 1 equiv) in 1 mL of THF was added at 0 °C. The reaction mixture was stirred at 45 °C for 3 days, and the reaction was quenched with saturated NaHCO$_3$. The aqueous phase was extracted three times with CH$_2$Cl$_2$. The combined organic layers were washed with a 2.5 N solution of Na$_2$S$_2$O$_3$ (10 mL) and brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. After chromatography on silica (4:1 hexane:EtOAc), **10** was obtained in 56% yield (0.027 g). *Procedure C*.[22] This procedure is analogous to the one utilized for the conversion of leurosine **1** to anhydrovinblastine **4** (vide infra) starting from 16,18(*S*)-dicarboxymethoxy-3(*R*),4(*S*)-epoxydihydrocleavamine **11** (0.13 g, 0.31 mmol, 1 equiv), Cp$_2$TiCl$_2$ (0.195 g, 2.5 equiv), and Zn (0.1 g, 5 equiv). After chromatography on silica (4:1 hexane/EtOAc), 16,-18(*S*)-dicarboxymethoxycleavamine **10** was obtained in 43% yield (0.054 g).

Procedure for the Synthesis of Anhydrovinblastine (4) from Leurosine (1). To a mixture of Cp$_2$TiCl$_2$ (0.325 g, 2.5 equiv) and powdered Zn (0.170 g, 5.0 equiv) in a flame-dried flask was added THF (5 mL). The solution was degassed under vacuum and purged with nitrogen (this operation was repeated three times). The heterogeneous solution was stirred vigorously for 45 min at room temperature. To the green slurry of Cp$_2$TiCl was added dropwise leurosine **1** (0.42 g, 0.52 mmol, 1 equiv) in 10 mL of THF. The solution was degassed under vacuum and purged with nitrogen (this operation was repeated three times). After 15 min, the mixture was filtered over paper and the reaction quenched with 1 N HCl. The solution was basified to pH 8 with saturated NaHCO$_3$. The precipitate was filtered through a fritted glass funnel, and the aqueous layer was extracted three times with Et$_2$O. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography over silica (96:4 CH$_2$Cl$_2$/MeOH) to afford anhydrovinblastine[23] **4** in 70% yield (0.288 g, amorphous powder): ^{1}H NMR δ 0.80 (t, *J* = 7.3 Hz, 3H), 0.98 (t, *J* = 7.6 Hz, 3H), 1.21−1.37 (m, 2H), 1.74−1.84 (m, 2H), 1.92 (q, *J* = 7.6 and 14.9 Hz, 2H), 2.10 (s, 3H), 2.08−2.15 (m, 1H), 2.36−2.47 (m, 2H), 2.55 (d, *J* = 13.4 Hz, 1H), 2.67 (s, 1H), 2.70 (s, 3H), 2.82 (d, *J* = 16.5 Hz, 1H), 2.96−3.11 (m, 2H), 3.17−3.39 (m, 6H), 3.52 (d, *J* = 16.5 Hz, 1H), 3.61 (s, 3H), 3.72 (s, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 5.29 (s, 1H), 5.30 (d, *J* = 6.1 Hz, 1H), 5.45 (brs, 2H), 5.84 (dd, *J* = 4.0 and 10.1 Hz, 1H), 6.11 (s, 1H), 6.61 (s, 1H), 7.10−7.16 (m, 3H), 7.51 (d, *J* = 7.3 Hz, 1H), 8.01 (brs, 1H), 9.86 (brs, 1H); ^{13}C NMR δ 8.3, 12.2, 21.1, 25.9, 27.7, 29.6, 30.7, 32.9, 34.3, 38.3, 42.6, 44.5, 45.9, 50.3, 52.1, 52.2, 53.2, 54.4, 55.5, 55.9, 65.5, 76.4, 79.6, 83.3, 94.2, 110.4, 117.3, 118.3, 118.8, 121.2, 122.2, 122.8, 123.5, 123.8, 124.5, 129.4, 130.0, 131.0, 134.9, 140.0, 152.7, 158.0, 170.8, 171.6, 174.6.

Procedure for the Synthesis of Bisindole Alkaloid (14) from Leurosine (1). To a solution of leurosine **1** (0.19 g, 0.24 mmol, 1 equiv) and 2-methyl-2-propanethiol (0.26 mL, 10 equiv) in 4 mL of THF was added dropwise, over a period of 10 min, 2.3 mL of a solution of Cp$_2$TiCl (2.5 equiv) in THF (supernatant) prepared as described above. After 45 min, the reaction was quenched with 1 N HCl. The solution was basified to pH 8 with saturated NaHCO$_3$. The precipitate was filtered through a fritted glass funnel, and the aqueous layer was extracted three times with Et$_2$O. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography over silica (97:3 CH$_2$Cl$_2$/MeOH) to afford **14**[21] in 11% yield (0.021 g, amorphous powder): ^{1}H NMR δ 0.78 (t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H), 1.20−1.34 (m, 3H), 1.72−1.88 (m, 3H), 2.08 (s, 3H), 2.05−2.25 (m, 1H), 2.39−2.47 (m, 2H), 2.62 (brs, 2H), 2.71 (s, 3H), 2.79 (d, *J* = 16.5 Hz, 1H), 2.96−3.42 (m, 10H), 3.61 (s, 3H), 3.64−3.72 (m, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 5.28 (d, 1H, *J* = 4.9 Hz, 1H), 5.43 (s, 1H), 5.83 (dd, *J* = 4.3 and 10.4 Hz, 1H), 6.07 (s, 1H), 6.50 (s, 1H), 7.07−7.19 (m, 3H), 7.45 (d, *J* = 7.3 Hz, 1H), 8.01 (brs, 1H), 9.83 (brs, 1H); ^{13}C NMR δ 8.3, 11.0, 21.1, 22.7, 25.5, 30.7, 30.8, 32.2, 35.9, 36.2, 38.1, 41.4, 42.6, 44.5, 52.1, 52.6, 53.2, 54.9, 55.7, 57.0, 65.5, 67.8, 71.5, 76.3, 79.6, 83.1, 94.1, 110.5, 115.3, 118.0, 119.4, 119.6, 122.8, 123.1, 123.2, 124.6, 128.5, 129.8, 130.3, 134.9, 153.1, 157.9, 170.9, 171.6, 174.3; MS (CI/NH$_3$) 811 ((M + H)$^+$, 100); IR (KBr) 3464, 1738, 1615, 1502, 1460, 1233, 1039, 733; HRMS (FAB) calcd for C$_{46}$H$_{59}$N$_4$O$_9$ (M + H)$^+$ 811.4282, found 811.4280.

Procedure for the Synthesis of Bisindole Alkaloid (15) from Leurosine (1). The alkaloid **15** was prepared as described for **14** using leurosine **1** (0.08 g, 0.1 mmol, 1 equiv), ethyl acrylate (0.1 mL, 9 equiv), and 1 mL of a solution of Cp$_2$TiCl (2.5 equiv) in THF (supernatant) prepared as described above (added dropwise over a period of 40 min). After the usual workup, the crude product was purified by chromatography over silica (97:3 CH$_2$Cl$_2$/MeOH) to afford **15** in 8% yield (7.5 mg, amorphous powder): ^{1}H NMR δ 0.79 (t, *J* = 7.3 Hz, 3H), 0.84 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.31−1.48 (m, 2H), 1.56 (m, 1H), 173−1.96 (m, 5H), 2.09 (s, 3H), 2.15 (m, 2H), 2.33−2.55 (m, 4H), 2.62 (s, 1H), 2.69 (s, 3H), 2.75 (d, *J* = 10.2 Hz, 1H), 2.85 (m, 2H), 3.05 (m, 1H), 3.14−3.39 (m, 6H), 3.54 (m, 1H), 3.63 (s, 3H), 3.73 (s, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 4.14 (q, *J* = 7.1 Hz, 2H), 5.27 (d, *J* = 7.1 Hz, 1H), 5.46 (s, 1H), 5.83 (dd, *J* = 3.7 and 10.1 Hz, 1H), 6.09 (s, 1H), 6.49 (s, 1H), 7.08–7.16 (m, 3H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.97 (brs, 1H), 9.84 (brs, 1H); MS (ESI) 911 ((M + H)$^+$, 100); IR (KBr) 3468, 2966, 2878, 1736, 1615, 1503, 1459, 1372, 1242, 1040, 911, 732; HRMS (FAB) calcd for C$_{51}$H$_{66}$N$_4$O$_{11}$ (M + H)$^+$ 911.4806, found 911.4798.

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Supporting Information Available: Reproductions of ^{1}H NMR spectra of compounds **1**, **4**, **9**−**11**, **14**, and **15** and ORTEP of leurosine-methiodide **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[23] Szántay, C., Jr.; Balázs, M.; Bölcskei, H.; Szántay, C. *Tetrahedron* **1991**, *47*, 1265−1274.