k_{-i}/k_{iv}, which represents the relative reactivities of A toward PPh_3 or H_2, is about thirty. The greater reactivity of the tricoordinate intermediate toward the more basic phosphine is not surprising although the ratio of 30 is higher than that previously estimated.[4,6]

In accord with the above discussion, the first-order rate constant for the reaction of $H_2RhCl(PPh_3)_2$ with CO to give $RhCl(CO)(PPh_3)_2$ would represent the *upper limit* for unimolecular H_2 elimination from this adduct in benzene, i.e., k_{-iv}. If indeed $k_{-iv} \leq 2.6\ s^{-1}$, several other numerical parameters can be calculated for the model described in Scheme II. First, the equilibrium constant K_{iv} for H_2 addition to A (k_{iv}/k_{-iv}) would be $\geq 4 \times 10^4\ M^{-1}$ (23 °C), somewhat larger than the value reported for K_{ii} ($6.4 \times 10^3\ M^{-1}$, 25 °C).[24] Second, given that the relationship $K_{iii} = K_iK_{iv}/K_{ii}$ must hold, the values of K_i and K_{iv} described here plus the reported value of K_{ii} would give a $K_{iii} \geq 1.4 \times 10^{-6}$ M, surprisingly larger than K_i (2.7×10^{-7} M). In addition, the rate constant k_{iii} for PPh_3 dissociation from $H_2RhCl(PPh_3)_2$ has been reported[6] from NMR exchange experiments to be $500\ s^{-1}$ in 25 °C (CH_2Cl_2). If it is assumed that the rates are little affected by the solvent differences, a k_{-iii} limit of $\leq 4 \times 10^8\ M^{-1}\ s^{-1}$ results. This value would appear to be rather high, although the reaction represented is between an unsaturated d^6 complex and a two-electron donor. The reported[6] k_{iii} also appears high for the dissociation of a two-electron donor from Rh(III), although this might be explainable by the probable position of the labilized phosphine being trans to a hydride ligand.

In summary, the above flash photolysis studies have successfully interrogated the quantitative reaction dynamics of the tricoordinate intermediate $RhCl(PPh_3)_2$ and related reactive intermediates. These results have proved consistent with the generally accepted mechanism for the $RhCl(PPh_3)_3$ catalysis of alkene hydrogenation but have provided a much firmer experimental basis for proposed reactivities of several key intermediates.

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Registry No. $RhCl(CO)(PPh_3)_2$, 13938-94-8; $RhCl(PPh_3)_2$, 68932-69-4; $RhCl(PPh_3)_3$, 14694-95-2; $H_2RhCl(PPh_3)_2$, 12119-41-4; $RhCl(C_2H_4)(PPh_3)_2$, 12120-14-8; $[RhCl(PPh_3)_2]_2$, 14653-50-0; $IrCl(CO)(PPh_3)_2$, 14871-41-1; $IrCl(PPh_3)_2$, 31690-54-7; CO, 630-08-0; PPh_3, 603-35-0; C_2H_4, 74-85-1; H_2, 1333-74-0; D_2, 7782-39-0; $IrCl(PPh_3)_3$, 16070-58-9.

(24) This value of K_{ii} is taken from ref 6 but corrected from that reported (9×10^3 M) owing to that source's use of a different solubility for H_2 in benzene (0.002 mol L^{-1} atm^{-1}) than used here (0.0028 mol L^{-1} atm^{-1}) (taken from ref 12).

Synthesis of (±)-Catharanthine, (+)-Anhydrovinblastine, and (−)-Anhydrovincovaline

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Abstract: An efficient total synthesis of (±)-catharanthine (**1**) has been accomplished. Diels–Alder reaction of **8** with α-chloroacryloyl chloride followed by reaction with MeOH gave **9**. Treatment of **9** with Me_3SiI gave **10**, and reaction of **10** with indole-3-acetyl chloride provided **11**, which was converted to **13**. Irradiation of **13** in CH_3CN/H_2O with a 450-W Hanovia mercury lamp through a Pyrex filter provided **14**. Reduction of **14** by treatment with Et_3OBF_4 and $NaBH_3CN$ gave (±)-catharanthine (**1**). The coupling of synthetic (±)-catharanthine with natural (−)-vindoline (**2**) via modified Polonovski reaction provided (+)-anhydrovinblastine (**15a**) and (−)-anhydrovincovaline (**17a**), which could be easily separated by flash chromatography.

The dimeric *Catharanthus* alkaloids vinblastine (**3a**) and vincristine (**3b**) are efficacious, clinically useful anticancer agents which are used routinely for the treatment of a number of human cancers.[2] These compounds have been shown to block mitosis with metaphase arrest by binding to the cell protein tubulin and preventing the assembly of microtubules.[2] Unfortunately, the isolation and purification of these compounds is a difficult process. For example, vincristine (**3b**) constitutes only 0.00025% of the dry weight of the leaves of *Catharanthus roseus* and must be separated from over sixty other alkaloids.[3]

It has recently become possible to prepare **3a** and **3b** with the correct C(16′*S*) configuration. The coupling of (+)-catharanthine (**1**) and (−)-vindoline (**2**), both obtained from *Catharanthus roseus*, gives (+)-anhydrovinblastine (**15a**); subsequent elaboration of **15a** provides **3a** and **3b**.[4] Although (−)-vindoline is the major alkaloid in *Catharanthus roseus* and is readily isolated and purified,[5] this approach is severely limited since (+)-catharanthine is only a minor constituent and is substantially more difficult to

(1) Fellow of the Alfred P. Sloan Foundation (1980–1984). Recipient of an NIH Research Career Development Award CA 00864 (1983–1988).

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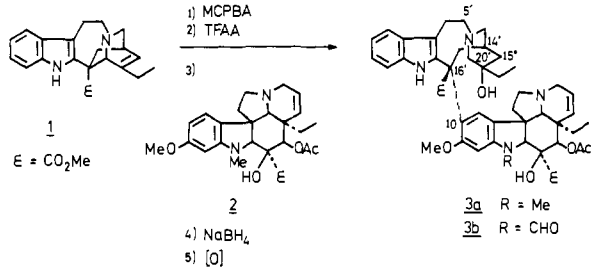
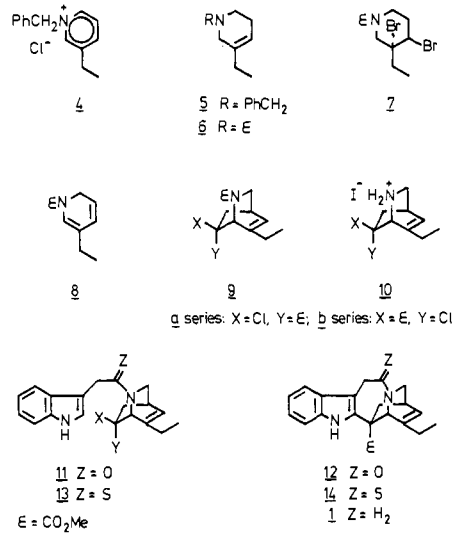
obtain and purify.[6] An attractive solution to this problem would involve the coupling of synthetic catharanthine with readily available natural (−)-vindoline. Thus, the development of an efficient method for total synthesis of catharanthine[7] holds the key to the preparation of semisynthetic vinblastine (**3a**) and vincristine (**3b**). It also opens the possibility for the synthesis of a variety of dimeric analogues.



Results and Discussion

Total Synthesis of (±)-Catharanthine.[8] The key step in our strategy for the synthesis of (±)-catharanthine (**1**) called for the Diels–Alder reaction of 1-carbomethoxy-5-ethyl-1,2-dihydropyridine (**8**) with a suitable dienophile to give an appropriately substituted isoquinuclidine. Since isoquinuclidines have been previously prepared by the reaction of 1-carboalkoxy-1,2-dihydropyridines,[9] this approach is limited by the availability of the requisite dihydropyridine **8**.

An excellent procedure for the synthesis of 1-carbomethoxy-1,2-dihydropyridine by the reaction of pyridine, methyl chloroformate, and $NaBH_4$ has been developed.[9a] Unfortunately, reaction of 3-ethylpyridine by this procedure affords 1-carbomethoxy-3-ethyl-1,2-dihydropyridine,[10] the incorrect regioisomer for a synthesis of catharanthine. Thus, the preparation of **8** by an oxidative process from the tetrahydropyridine **6** was examined. We had previously prepared a 1-acyl-5-ethyl-1,2-dihydropyridine by a bromination–double dehydrobromination sequence.[11] This strategy also proved useful for the preparation of **8** from 3-ethylpyridine.[12] Reaction of 3-ethylpyridine with benzyl chloride gave 1-benzyl-3-ethylpyridinium chloride (**4**) which was reduced with $NaBH_4$ in ethanol to provide 1-benzyl-3-ethyl-1,2,5,6-tetrahydropyridine (**5**). Debenzylation of **5** by treatment with methyl chloroformate provided 1-carbomethoxy-3-ethyl-1,2,5,6-tetrahydropyridine (**6**). Reaction of **6** with Br_2 gave the dibromide **7**, and double dehydrobromination of **7** with $EtAlCl_2$ in HMPA gave 1-carbomethoxy-5-ethyl-1,2-dihydropyridine (**8**).[12] This extremely mild double dehydrobromination procedure is crucial for the preparation of **8**, since the use of other reagents, including quinoline, 1,4-diazabicyclo[2.2.2]octane, or 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), was not successful. The $EtAlCl_2$ appears to be functioning as both a Lewis acid to assist in weakening the carbon–bromine bond toward heterolytic cleavage and as an acid scavenger[13] to consume the liberated hydrogen bromide.



Initially, the Diels–Alder reaction was carried out between **8** and methyl α-chloroacrylate to give a 1:1.4 mixture of the isomers **9a** and **9b** in 96% yield.[8] Subsequently, it was found more advantageous to conduct the Diels–Alder reaction between **8** and α-chloroacryloyl chloride followed by treatment with methanol and triethylamine. This procedure afforded a 3:1 endo/exo ratio of **9a**:**9b** in 90% overall yield. Treatment of the 3:1 mixture of **9a** and **9b** with excess freshly prepared trimethylsilyl iodide[14] gave a mixture of **10a** and **10b**.

Although it is possible to separate **9a** and **9b** by flash chromatography,[15] this is unnecessary for the synthesis of **1**. A comparison of the relative change in the chemical shifts for the methyl ester singlet in the carbamate **9** and the hydrogen iodide salt **10** allows the assignment of endo/exo stereochemistry.[16] Thus, reaction of trimethylsilyl iodide with a pure sample of **9a** gave **10a**, and reaction of a pure sample of **9b** gave **10b**. The chemical shifts for the methyl esters in **9a** and **10a** differed by less than 0.05 ppm, whereas they differed by 0.4 ppm for **9b** and **10b**. The ability of **10b** to undergo intramolecular hydrogen bonding between the ammonium group and the methyl ester presumably causes the larger change in chemical shift. It is also noteworthy that **10b** is considerably less stable than **10a**, presumably due to iodide-mediated cleavage of the methyl ester assisted by intramolecular protonation by the ammonium salt.

The mixture of **10a** and **10b** was reacted without purification first with *O,N*-bis(trimethylsilyl)acetamide[17] and then with indole-3-acetyl chloride[18] to provide the indoles **11a** and **11b** as a 3:1 mixture of isomers in 97% overall yield from **9**. The *O,N*-bis(trimethylsilyl)acetamide functions as an acid scavenger in this reaction, and the acylation may proceed via the *N*-silylamine corresponding to **10**.[17] The above transformations were also carried out on pure samples of **9a** and **9b** in order to obtain pure samples

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of **11a** and **11b**. Interestingly, solutions of pure **11a** or **11b** in $CDCl_3$ were found to equilibrate to a 1:1 mixture of **11a** and **11b** when exposed to catalytic amounts of anhydrous HCl.

Numerous attempts to effect photochemical cyclization[19] by irradiation of dilute solutions of **11a** or **11b** (or mixtures of **11a** and **11b**) in CH_3CN/H_2O or $MeOH/H_2O$ containing $NaHCO_3$ with a 450-W Hanovia mercury lamp, with or without Pyrex or Vycor filters, afforded a complex mixture of products which contained only trace amounts of **12**, despite the fact that the corresponding 20-deethyl compound (mixture of endo/exo isomers) provides 5-oxo-20-deethylcatharanthine in moderate yield under these reaction conditions.[20] Although the factors responsible for the difference in behavior of **11** and 20-deethyl analogue are not certain, conformational preferences or solubility properties may be involved.

Reaction of the 3:1 mixture of **11a** and **11b** with Lawesson's reagent[21] provided a 79% yield of the thioamide exclusively as the endo-isomer **13a**. Interestingly, although attempts to convert a pure sample of **11b** to a thioamide with either Lawesson's reagent or P_2S_5 were not successful, when a 1:1.4 mixture of **11a** and **11b** was reacted with Lawesson's reagent in dimethoxyethane containing a catalytic amount of anhydrous HCl, the thioamide **13a** was obtained in 70% yield, presumably via isomerization of **11b** to **11a** and subsequent thionation.

Irradiation of a dilute solution of **13a** in CH_3CN/H_2O containing $NaHCO_3$ with a 450-W Hanovia mercury lamp through a Pyrex filter for 6 h provided **14** in 41% yield. The yield in the photochemical cyclization of **13a** to **14** was improved over our initial communication[8] by the slow addition of a solution of **13a** to the photochemical apparatus via syringe pump. The thiolactam **14** was reduced[22] by treatment with Et_3OBF_4 followed by $NaBH_3CN/HOAc$ to provide (±)-catharanthine (**1**) in 27% yield from **13a** and an overall yield of 12% from 3-ethylpyridine.

Coupling of (±)-Catharanthine with (−)-Vindoline. Four diastereomers are theoretically possible from the coupling between C(16) of (±)-catharanthine and C(10) of (−)-vindoline.[23] It has been shown, however, that the coupling of (+)-catharanthine with (−)-vindoline under properly controlled conditions gives only (+)-anhydrovinblastine (**15a**) with the natural C(16′*S*,14′*R*) configuration, and that and that none of the C(16′*R*,14′*R*)-diastereomer **16a** is formed.[4] Although the coupling of (−)-catharanthine and (−)-vindoline could produce the C(16′*R*,14′*S*)-diastereomer **17a** and the C(16′*S*,14′*S*)-diastereomer **18a**, the formation of **17a** should predominate for the same stereoelectronic factors which favor the formation of **15a** over **16a**. Indeed, it has been reported that the coupling of (±)-20-deethylcatharanthine with (−)-vindoline gave **15b** and **17b**, and none of the diastereomers **16b** and **18b** were detected.[24]

15 X = E, Y = V
16 X = V, Y = E
a series: R = Et; **b** series: R = H
E = CO_2Me, V = 10-Vindolinyl

17 X = E, Y = V
18 X = V, Y = E

We have found that the coupling of our synthetic (±)-catharanthine with (−)-vindoline by the modified Polonovski reaction[4] gave the (16′*S*,14′*R*) diastereomer, (+)-anhydrovinblastine (**15a**), which results from the coupling of (+)-catharanthine and (−)-vindoline, in 46% yield based on (+)-catharanthine. The (16′*R*,14′*S*) diastereomer, (−)-anhydrovincovaline (**17a**), which results from the coupling of (−)-catharanthine with (−)-vindoline, was also isolated in 54% yield based on (−)-catharanthine. There was no evidence for the formation of other diastereomeric dimers. The circular dichroism (CD) spectra for systems related to **15**, **16**, **17**, and **18** are quite characteristic and allow for the assignment of configuration at C(16′) and C(14′).[4,24,25] Finally, it should be emphasized that since (+)-anhydrovinblastine (**15a**) and (−)-anhydrovincovaline (**17a**) are easily separated by flash chromatography, there is no need to resolve the synthetic (±)-catharanthine prior to coupling.

Experimental Section

Gas chromtography was conducted with a 12-m DB-5 fused-quartz capillary column. HPLC was conducted with a 4.6 mm ID by 25 cm Altex 5 μm ultrasphere ODS column. Flash chromatography was performed with silica gel 60, 40–63 μm (E. Merck).[15]

1-Benzyl-3-ethylpyridinium Chloride (4). A mixture of 3-ethylpyridine (29.7 g, 319 mmol) and benzyl chloride (40.7 g, 320 mmol) was left standing under argon at 20 °C for 72 h. The resulting white solid was powdered, washed with Et_2O, and then dried in vacuo to give **4** (70.1 g, 300 mmol) in 94% yield: mp 152–153 °C; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.32 (t, *J* = 7 Hz, 3 H), 2.95 (dd, *J* = 7 Hz, 2 H), 6.43 (s, 2 H), 7.2–7.5 (m, 3 H), 7.7–8.5 (m, 4 H), 9.85 (d, *J* = 6 Hz, 1 H), 10.2 (br s, 1 H).

1-Benzyl-3-ethyl-1,2,5,6-tetrahydropyridine (5). To a suspension of $NaBH_4$ (2.38 g, 68.4 mmol) in absolute EtOH (60 mL) at 0 °C was added dropwise a solution of **4** (4.00 g, 17.1 mmol) in absolute EtOH (25 mL) over 15 min. The mixture was then stirred at 0 °C for 3 h, warmed to 25 °C, and stirred for 21 h. The EtOH was evaporated in vacuo, H_2O (150 mL) was added to dissolve the salts, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo. Distillation of the residue (bp 150 °C (0.1 mm)) gave **5** (3.43 g, 17.1 mmol) in 100% yield as a pale yellow liquid of >97% purity by capillary GC: ^1H NMR ($CDCl_3$, 60 MHz) δ 0.97 (t, *J* = 7 Hz, 3 H), 1.6–2.3 (m, 4 H), 2.51 (t, *J* = 5 Hz, 2 H), 2.84 (d, *J* = 2 Hz, 2 H), 3.55 (s, 2 H), 5.4 (br s, 1 H), 7.32 (s, 5 H).

1-Carbomethoxy-3-ethyl-1,2,5,6-tetrahydropyridine (6). A solution of **5** (1.92 g, 9.54 mmol) and methyl chloroformate (1.5 mL, 19 mmol) in benzene (20 mL) was heated at reflux for 5 h. The benzene was evaporated in vacuo, and the remaining liquid was distilled through a 10-cm Vigreux column. The first fraction (bp 32 °C (0.4 mm)) was benzyl chloride. The second fraction (bp 77 °C, 0.40 mm) provided **6** (1.34 g, 7.93 mmol) in 83% yield as a colorless liquid: ^1H NMR ($CDCl_3$, 60 MHz) δ 1.0 (t, *J* = 7 Hz, 3 H), 1.7–2.3 (m, 4 H), 3.40 (t, *J* = 6 Hz, 2 H), 3.60 (s, 3 H), 3.70 (d, *J* = 2 Hz, 2 H), 5.45 (br s, 1 H).

1-Carbomethoxy-*trans*-3,4-dibromo-3-ethylpiperidine (7). To a solution of **6** (724 mg, 4.29 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added a solution of Br_2 (685 mg, 4.29 mmol) in CH_2Cl_2 (5 mL). When the orange color persisted the solution was stirred an additional 2 min, and one drop of cyclohexene was added. The solvent was evaporated in vacuo, and the residue was purified by flash chromatography (50% Et_2O/hexane) to give **7** (1.26 g, 3.83 mmol) in 89% yield as a clear liquid which solidified on standing. Crystallization from acetone/H_2O gave white needles: mp 56–58 °C; ^1H NMR ($CDCl_3$, 80 MHz) δ 1.1 (t, *J* = 7 Hz, 3 H), 3.5–1.7 (m, 6 H), 3.7 (s, 3 H), 3.8–4.3 (m, 2 H), 4.6 (m, 1 H); IR ($CHCl_3$, cm^{-1}) 1710, 1470, 1450, 1240.

1-Carbomethoxy-3-ethyl-1,6-dihydropyridine (8). To a solution of **7** (1.70 g, 5.18 mmol) in HMPA (15 mL) at 0 °C was added a 25% w/w solution of $EtAlCl_2$ in hexane (2.0 g, 8.8 mL, 16 mmol). The ice bath was removed, and the reaction was stirred under argon at 60 °C for 1.5 h. The reaction solution was cooled to 0 °C, quenched by the slow addition of ice-cold H_2O (50 mL), and extracted with Et_2O (3 × 25 mL). The combined Et_2O extracts were washed with H_2O (2 × 25 mL) and brine (50 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo to give **8** (0.82 g) as a pale yellow liquid of 88% purity by capillary GC. This compound is not stable to chromatography or distillation and should be used immediately. ^1H NMR ($CDCl_3$, 80 MHz) δ 1.0 (t, *J* = 7 Hz, 3 H), 2.0 (m, 2 H), 3.7 (s, 3 H), 4.3 (dd, *J* = 3, 1 Hz, 2 H), 5.6–5.9 (m, 2 H), 6.5 (m, 1 H); MS, *m/e* 167 (M^+), 166, 152, 122, 107, 93, 59; UV (EtOH, λ_{max}) 300 nm (ε 5600).

(±)-1α,4α-2-Azabicyclo[2.2.2]oct-7-ene-6α-chloro-7-ethyl-2,6-dicarboxylic Acid Dimethyl Ester (9a) and (±)-1α,4α-2-Azabicyclo-

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[2.2.2]oct-7-ene-6β-chloro-7-ethyl-2,6-dicarboxylic Acid Dimethyl Ester (9b). Method 1. A solution of crude **8** (1.14 g, 88% pure, 6.0 mmol), methyl α-chloroacrylate (1.45 g, 12.0 mmol), and hydroquinone (45 mg, 0.4 mmol) in dry toluene (3 mL) was heated at 95 °C with stirring for 22 h. The toluene and excess methyl α-chloroacrylate were evaporated in vacuo, and the resulting viscous liquid was purified by flash chromatography (95% CH_2Cl_2/Et_2O) to yield a 1:1.4 mixture of **9a** to **9b** (1.60 g, 5.57 mmol) as a pale yellow liquid in 93% yield: IR ($CHCl_3$, cm^{-1}) 1760, 1723, 1465, 1404; MS, *m/e* 289 (M^+, ^{37}Cl), 287 (M^+, ^{35}Cl), 258, 256, 230, 228, 168, 167, 166, 152, 122, 108, 107. Pure samples of **9a** and **9b** could be obtained by repeated careful flash chromatography (95% CH_2Cl_2/Et_2O). The NMR of these compounds is complicated by the presence of carbamate rotomers. **9a**: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.0 (overlapping t, J = 7 Hz, 3 H), 1.96 (dd, J = 13, 8 Hz, 1 H), 2.2 (m, 2 H), 2.8 (m, 2 H), 3.0 (m, 1 H), 3.41 (t, J = 8.5 Hz, 1 H), 3.73 (s), 3.75 (s), 3.7 (s), and 3.80 (s) (total 6 H), 4.93 (s, 0.5 H), 5.13 (s, 0.5 H), 6.0 (m, 1 H). **9b**: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.1 (overlapping t, J = 7 Hz, 3 H), 1.19 (m, 1 H), 2.3 (m, 2 H), 2.9 (m, 2 H), 3.1 (m, 1 H), 3.7 (m, 7 H), 5.1 (m, 1 H), 6.1 (m, 1 H).

(±)-1α,4α-2-Azabicyclo[2.2.2]oct-7-ene-6α-chloro-7-ethyl-2,6-dicarboxylic Acid Dimethyl Ester (9a) and (±)-1α,4α-2-Azabicyclo-[2.2.2]oct-7-ene-6β-chloro-7-ethyl-2,6-dicarboxylic Acid Dimethyl Ester (9b). Method 2. To a solution of α-chloroacrylic acid (770 mg, 7.23 mmol) in dry Et_2O (50 mL) at 0 °C was added PCl_5 (1.66 g, 7.95 mmol). The cloudy mixture was stirred for 40 min until the PCl_5 had dissolved. The Et_2O was evaporated in vacuo to give a mixture of α-chloroacryloyl chloride and $POCl_3$, which codistill at 98–105 °C, as a colorless liquid: ^1H NMR ($CDCl_3$, 80 MHz) δ 6.58 (d, J = 2.5 Hz, 1 H), 7.1 (d, J = 2.5 Hz, 1 H); IR ($CHCl_3$, cm^{-1}) 1775, 1617, 1310 (P=O). Dry toluene (1 mL) was added to this mixture of α-chloroacryloyl chloride and $POCl_3$, the solution was cooled to 0 °C under argon, and a solution of crude **8** (0.334 g, 83% pure, 1.66 mmol) in dry toluene (1.75 mL) was slowly added at 0 °C. The reaction solution was stirred at 0 °C for 2 h and then at 25 °C for 12 h. The reaction was quenched with 20% Et_3N/MeOH (15 mL), H_2O (100 mL) was added, and the mixture was extracted with Et_2O (3 × 50 mL). The combined Et_2O extracts were dried ($MgSO_4$), the solvents were removed in vacuo, and the resulting viscous liquid was purified by flash chromatography (95% CH_2Cl_2/Et_2O) to give a 3:1 mixture of **9a** and **9b** (427 mg, 1.49 mmol) in 90% yield.

Indole-3-acetyl Chloride. Indole-3-acetic acid (2.0 g, 11.5 mmol) and PCl_5 (2.87 g, 13.8 mmol) were combined in dry Et_2O (60 mL) at 0 °C under argon and stirred at 0 °C for 30 min until the solids dissolved. Approximately 75% of the Et_2O was evaporated in vacuo, cold (0 °C) hexane (150 mL) was added, and the solution was filtered. The filtrate was cooled to −78 °C, and the crystals which formed were collected to provide indole-3-acetyl chloride (1.78 g, 9.10 mmol) as colorless flakes in 80% yield: mp 63–65 °C (lit.[18] mp 68 °C); ^1H NMR ($CDCl_3$, 80 MHz) δ 4.25 (s, 2 H), 6.9–7.3 (m, 4 H), 7.4–7.6 (m, 1 H), 7.95 (br s, 1 H); IR ($CHCl_3$, cm^{-1}) 3490, 1806, 1467, 1428.

(±)-1α,4α-2-Azabicyclo[2.2.2]oct-7-ene-6α-chloro-7-ethyl-6-carboxylic Acid Methyl Ester Hydrogen Iodide Salt (10a) and (±)-1α,4α-2-Azabicyclo[2.2.2]oct-7-ene-6β-chloro-7-ethyl-6-carboxylic Acid Methyl Ester Hydrogen Iodide Salt (10b). A mixture of I_2 (952 mg, 3.75 mmol) and hexamethyldisilane (1.10g, 7.50 mmol) was heated at 120 °C under argon with stirring until a colorless solution resulted (15 min). The solution was cooled to 25 °C, and a 3:1 mixture of **9a** and **9b** (0.98 g, 3.41 mmol) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred at 25 °C for 12 h and quenched with MeOH (10 mL), and the solvents were evaporated in vacuo to yield a mixture of hydrogen iodide salts **10a** and **10b** (1.22 g, 3.41 mmol) as an orange foam: IR ($CHCl_3$, cm^{-1}) 3030–2600, 1765, 1755. Reaction of a pure sample of **9a** by the same procedure gave **10a**: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.05 (t, J = 8.5 Hz, 3 H), 2.02 (dd, J = 14, 2.5 Hz, 1 H), 2.16 (m, 1 H), 2.35 (m, 1 H), 2.75 (dt, J = 14, 3 Hz, 1 H), 2.78 (d, J = 8.5 Hz, 1 H), 2.8 (br s, 1 H), 3.23 (d, J = 8.5 Hz, 1 H), 3.79 (s, 3 H), 4.15 (s, 1 H), 6.14 (d, J = 7.6 Hz, 1 H), 7.5 (br s, 2 H). Reaction of a pure sample of **9b** by the same procedure gave **10b**: ^1H NMR ($CDCl_3$, 80 MHz) δ 1.15 (t, J = 7 Hz, 3 H), 1.7–3.5 (m, 6 H), 4.0 (s, 3 H), 4.67 (m, 1 H), 4.93 (m, 1 H), 6.4–6.1 (m, 1 *H*), 8.1 (br s, 1 H), 9.0 (br s, 1 H). The HI salt **10b** is not very stable at 25 °C, presumably due to iodide-mediated cleavage of the methyl ester assisted by intramolecular protonation from the ammonium salt.

(±)-1α,4α-2-Azabicyclo[2.2.2]oct-7-ene-2-[1-(2-(indol-3-yl)-1-oxoethyl)]-6α-chloro-7-ethyl-6-carboxylic Acid Methyl Ester (11a) and (±)-1α,4α-2-Azabicyclo[2.2.2]oct-7-ene-2-[1-(2-(indol-3-yl)-1-oxoethyl)]-6β-chloro-7-ethyl-6β-carboxylic Acid Methyl Ester (11b). The crude hydrogen iodide salts **10a** and **10b** (1.22 g, 3.41 mmol) were dissolved in CH_2Cl_2 (15 mL) to give a deep red solution. The solution was cooled to 0 °C under argon, and bis(trimethylsilyl)acetamide (1.53 g, 7.50 mmol) was added rapidly, causing the solution to become pale yellow. The solution was stirred for 30 min at 0 °C, and then a solution of indole-3-acetyl chloride (1.32 g, 6.82 mmol) in CH_2Cl_2 (5 mL) was added. The ice bath was removed and the reaction stirred an additional 3 h at 25 °C. The CH_2Cl_2 solution was washed with an aqueous solution which was 1 M in $NaHCO_3$ and 0.5 M in KF (2 × 25 mL) and dried ($MgSO_4$), and the solvents were removed in vacuo to give a dark foam (1.65 g), which was purified by flash chromatography (75% CH_2Cl_2/EtOAc) to provide a 3:1 mixture of **11a** and **11b** (1.20 g, 3.10 mmol) in 91% yield as an off-white foam: mp 58–64 °C; IR ($CHCl_3$, cm^{-1}) 3800, 3110–2810, 1755, 1650, 1470, 1420; UV (EtOH, λ_{max}) 219.5 nm (ε 4600); HREIMS calcd for $C_{21}H_{23}ClN_2O_3$ 386.1395 (^{35}Cl), found 386.1367. The same procedure was utilized starting with a pure sample of **10a** to give **11a**. The NMR is complicated by the presence of a 1:1 mixture of rotamers: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.68 (t, J = 7.6 Hz, 1.5 H), 1.01 (t, J = 7.6 Hz, 1.5 H), 1.6 (m, 1 H), 1.90 (dd, J = 13.5, 3 Hz, 0.5 H), 1.97 (dd, J = 13.5, 3 Hz, 0.5 H), 2.15 (m, 1 H), 2.82 (m, 0.5 H), 2.79 (m, 0.5 H), 2.75 (m, 1 H), 3.07 (dt, J = 10, 4 Hz, 0.5 H), 3.12 (dt, J = 10, 4 Hz, 0.5 H), 3.53 (m, 1 H), 3.77 (s, 1.5 H), 3.74 (s, 1.5 H), 3.92 (d, J = 14 Hz, 1 H), 4.16 (d, J = 14 Hz, 1 H), 4.86 (d, J = 2 Hz, 0.5 H), 5.72 (d, J = 2 Hz, 0.5 H), 5.97 (m, 1 H), 7.0–7.2 (m, 3 H), 7.34 (d, J = 7, 1 H), 7.57 (d, J = 7 Hz, 0.5 H), 7.68 (d, J = 7 Hz, 0.5 H), 8.3 (overlapping singlets, 1 H). The same procedure was utilized starting with a pure sample of **10b** to give **11b** which was crystallized from chloroform/hexane, mp 136–140 °C. The NMR is complicated by the presence of a 2:1 mixture of rotomers: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, J = 7.5 Hz, 2 H), 1.2 (t, J = 7.5 Hz, 1 H), 2.0–2.5 (m, 4 H), 2.92 (q, J = 5 Hz, 0.3 H), 3.11 (t, J = 5 Hz, 0.7 H), 3.22 (d, J = 10.5 Hz, 0.7 H), 3.6–3.9 (m with s at 3.76 and 3.81, 6 H), 4.12 (d, J = 10.5 Hz, 0.3 H), 4.77 (br s, 0.3 H), 4.96 (br s, 0.7 H), 6.61 (s, 0.7 H), 6.67 (s, 0.3 H), 7.1 (m, 2 H), 7.17 (t, J = 8 Hz, 0.3 H), 7.18 (t, J = 8 Hz, 0.7 H), 7.32 (m, 1 H), 7.53 (d, J = 8 Hz, 0.7 H), 7.57 (d, J = 8 Hz, 0.3 H), 8.13 (br s, 0.3 H), 8.18 (br s, 0.7 H).

Photocyclization of 11a. A solution of **11a** (120 mg, 0.310 mmol) and $NaHCO_3$ (0.52 g, 6.2 mmol) in MeOH (112 mL) and H_2O (168 mL) in a 350-mL photochemical apparatus was purged with argon and irradiated with a 450-W medium-pressure mercury lamp through a Pyrex filter for 2 h at which time **11a** could no longer be detected by HPLC (80% CH_3CN/H_2O). The solvent volume was decreased by 30% in vacuo, saturated with NaCl, and extracted with CH_2Cl_2 (3 × 100 mL). The extracts were combined, dried ($MgSO_4$), and evaporated in vacuo to give a brown foam (120 mg). TLC (50% EtOAc/hexane) showed a streak of many compounds (R_f 0.15–0.70). Although attempts to isolate a pure sample of **12** by flash chromatography were not successful, a mixture containing **11a** and **12** (49 mg) was obtained from the fractions with $R_f > 0.45$. This mixture was reacted with Lawesson's reagent (34 mg, 0.080 mmol) in 1,2-dimethoxyethane (1 mL) at 80 °C under argon for 4 h. The 1,2-dimethoxyethane was removed in vacuo, and the residue was subjected to flash chromatography (95% CH_2Cl_2/EtOAc) to give an off-white foam (24 mg), which contained **14**, **13a**, and other unidentified compounds as indicated by ^1H NMR. The mixture was dissolved in THF (2 mL), methyl iodide (0.5 mL) was added, and the resulting solution was stirred at 25 °C for 10 h. The solution was evaporated in vacuo, and the residue was dissolved in MeOH (1 mL), cooled to 0 °C, and treated with $NaBH_3CN$ (26 mg, 0.41 mmol). The mixture was stirred for 10 min while warming to 25 °C, 25% HOAc/H_2O (0.5 mL) was added, and the reaction mixture was stirred at 25 °C for 5 h. The reaction mixture was treated with 5% aqueous NaOH (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were dried (K_2CO_3), the CH_2Cl_2 was removed in vacuo, and the resulting brown foam (28 mg) was purified by flash chromatography (75% CH_2Cl_2/EtOAc) to give (±)-catharanthine (**1**) (3 mg, 0.009 mmol). Similar results were obtained for the reaction of **11b** or mixtures **11a** and **11b** in either MeOH/H_2O or CH_3CN/H_2O.

(±)-1α,4α-2-Azabicyclo[2.2.2]oct-7-ene-2-[1-(2-(indol-3-yl)-1-thioxoethyl)]-6α-chloro-7-ethyl-6-carboxylic Acid Methyl Ester (13a). To a solution of a 3:1 mixture of amides **11a** and **11b** (320 mg, 0.829 mmol) in dry 1,2-dimethoxyethane (20 mL) under argon was added Lawesson's reagent (268 mg, 0.663 mmol, freshly recrystallized from toluene), and the mixture was stirred at 65 °C for 1 h. The solvent was removed in vacuo, CH_2Cl_2 was added, and the solution was washed with H_2O, dried ($MgSO_4$), and concentrated to give a brown foam. The solid was purified by flash chromatography (95% CH_2Cl_2/Et_2O) followed by crystallization from CH_3CN to give the thioamide **13a** (260 mg, 0.650 mmol) in 79% yield: mp 137–139 °C; IR ($CHCl_3$, cm^{-1}) 3495, 1760, 1460, 1440, 1270, 1170; HREIMS calcd for $C_{21}H_{22}ClN_2O_2S$ 402.1166, found 402.1155; ^1H NMR ($CDCl_3$, 500 MHz) (2:1 mixture of rotomers) δ 0.5 (t, J = 7.2, 2 H), 0.8 (d, J = 7.2, 0.7 H), 1.05 (t, J = 7.2, 1 H), 1.4 (d, J = 7.2, 0.7 H), 1.87 (dd, J = 13, 2 Hz, 1 H), 2.02 (d, J = 7.2, 0.3 H), 2.12 (d, J = 7.2, 0.3 H), 2.78 (m, 1 H), 2.8 (m, 0.3 H), 2.94 (m, 0.7 H), 3.23 (dt, J = 13.5, 2.5 Hz, 0.3 H), 3.45 (dt, J = 13.5, 2.5 Hz, 0.7 H), 3.68 (s, 2

H), 3.80 (s, 1 H), 3.57 (dd, J = 13.5, 2 Hz, 0.3 H), 3.84 (dd, J = 13.5, 2 Hz, 0.7 H), 4.70–4.25 (m, 2 H), 5.25 (d, J = 2 Hz, 1 H), 6.0 (m, 1 H), 7.3–6.9 (m, 3 H), 7.38 (d, J = 7.6 Hz, 1 H), 7.57 (d, J = 7.6 Hz, 0.3 H), 7.79 (d, J = 7.6 Hz, 0.7 H), 8.02 (br s, 0.3 H), 8.09 (br s, 0.7 H); UV (EtOH, λ_{max}) 220 nm (ϵ 17800), 274 nm (ϵ 9000).

Photocyclization of 13a to (±)-5-Thlooxocatharanthine (14). A solution of CH_3CN (88 mL), H_2O (212 mL), and $NaHCO_3$ (0.39 g, 4.7 mmol) in a 350-mL photochemical apparatus was degassed with argon and irradiated with a 450-W medium-pressure mercury vapor lamp through a Pyrex filter. A solution of **13a** (95.0 mg, 0.236 mmol) in CH_3CN (10 mL) was injected into the photochamber via syringe pump at 0.27 mL/min. The solution was irradiated an additional 6 h, at which time HPLC (80% CH_3CN/H_2O) indicated that no starting material remained. The solution was saturated with NaCl and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated in vacuo to give an off-white foam (76 mg) which was purified by flash chromatography (95% CH_2Cl_2/EtOAc) and crystallized from Et_2O to yield **14** (35.3 mg, 0.096 mmol) as white cubes in 41% yield: mp 233–235 °C; IR ($CHCl_3$, cm^{-1}) 3490, 3460, 1740; HREIMS calcd for $C_{21}H_{22}N_2O_2S$ 366.1399, found 366.1386; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.1 (t, J = 7 Hz, 3 H), 1.82 (d, J = 13.5 Hz, 1 H), 2.3 (q, J = 7 Hz, 2 H), 2.7 (m, 1 H), 3.0 (m, 1 H), 3.32 (d, J = 12.8 Hz, 1 H), 3.68 (s, 3 H), 3.97 (dd, J = 12.8, 4.3 Hz, 1 H), 4.55 (d, J = 7.7 Hz, 2 H), 5.5 (s, 1 H), 6.38 (dd, J = 7.3, 1.6 Hz, 1 H), 7.1–7.2 (m, 2 H), 7.26 (d, J = 8 Hz, 1 H), 7.6 (d, J = 8 Hz, 1 H), 8.0 (br s, 1 H).

(±)-Catharanthine (1). To a solution of **14** (0.20 g, 0.545 mmol) in dry CH_2Cl_2 (4 mL) cooled to 0 °C under argon was added a 1.0 M solution of Et_3OBF_4 in CH_2Cl_2 (2.8 mL, 0.709 mmol), and the solution was stirred for 30 min. The CH_2Cl_2 was evaporated in vacuo, MeOH (8 mL) was added, the solution was cooled to 0 °C, and $NaBH_4$ (0.206 g, 3.27 mmol) was added slowly. The mixture was stirred for 15 min, 50% MeOH/acetic acid (4 mL) was added, and the solution was stirred at 25 °C for 4 h. The reaction mixture was poured into 5% aqueous NaOH (100 mL) and extracted with Et_2O (50 mL), CH_2Cl_2 (50 mL), and again with Et_2O (50 mL). The combined organic extracts were dried (K_2CO_3) and the solvent was evaporated in vacuo to give crude **1** (172 mg) as an off-white solid, which was further purified by flash chromatography (50% CH_2Cl_2/EtOAc) and crystallization from Et_2O to yield (±)-catharanthine (**1**) (120 mg, 0.360 mmol) as white cubes in 65% yield: mp 163–164 °C (lit.[7a] mp 61–63 °C from MeOH; lit.[7c] mp 175–176 °C dec from MeOH); IR ($CHCl_3$, cm^{-1}) 3460, 3500–3300, 1740, 1460, 1440, 1250, 1140; HREIMS calcd for $C_{21}H_{24}N_2O_2$ 336.1838, found 336.1839; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.08 (t, J = 7 Hz, 3 H), 1.79 (dd, J = 12, 2.5 Hz, 1 H), 2.12 (m, 1 H), 2.33 (m, 1 H), 2.73 (dd, J = 7, 2 Hz, 2 H), 2.86 (m, 2 H), 2.93 (dt, J = 14, 7.5 Hz, 1 H), 3.29 (ddd, J = 14, 9, 3.6 Hz, 1 H), 3.37 (dt, J = 11, 4 Hz, 1 H), 3.57 (ddd, J = 11, 9, 3.6 Hz, 1 H), 3.72 (s, 3 H), 4.18 (s, 1 H), 5.94 (dd, J = 7, 1.5 Hz, 1 H), 7.1 (t, J = 7 Hz, 1 H), 7.15 (dd, J = 7, 8 Hz, 1 H), 7.24 (d, J = 8 Hz, 1 H), 7.49 (d, J = 7 Hz, 1 H), 7.65 (br s, 1 H).

(±)-Anhydrovinblastine [(+)-$\Delta^{15'}$20'-Dehydroxyvinblastine] (15a) and (−)-Anhydrovincolvaline [(−)-$\Delta^{15'}$20'-Dehydroxyvincolvaline] (17a) by the Polonovski Coupling (±)-Catharanthine (1) with (−)-Vindoline (2). To a solution of (±)-catharanthine (31.6 mg, 0.094 mmol) in dry CH_2Cl_2 (1 mL) cooled to −3 °C was added 100% *m*-chloroperoxybenzoic acid (18.7 mg, 0.108 mmol). The solution was stirred for 10 min, a solution of (−)-vindoline (47.2 mg, 0.103 mmol) in dry CH_2Cl_2 (1 mL) was added, and the solution was cooled to −42 °C at which time a precipitate formed. Trifluoroacetic anhydride (118 mg, 0.56 mmol) was added rapidly via microsyringe, the precipitate dissolved and the color of the reaction mixture changed from pale yellow to deep burgundy within 15 min. The solution was stirred at −42 °C for 3 h, and the cold solution was poured into a solution of EtOH (5 mL) and $NaBH_4$ (250 mg). Water (20 mL) was added, and the solution was extracted with chloroform (3 × 15 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the solvent was removed in vacuo to yield a light brown foam (80 mg) which was purified by flash chromatography (15% MeOH/EtOAc). The first fractions contained a mixture of **17a** and unreacted (−)-vindoline. Isolation of subsequent fractions and crystallization from MeOH provided (+)-anhydrovinblastine (**15a**) (17.0 mg, 0.0214 mmol) in 46% yield based on (+)-catharanthine: mp 208–211 °C; (lit.[4f] mp 208–210 °C; lit.[4i] mp 171–173 °C); $[\alpha]_D^{22}$ +19° (c 0.34 $CHCl_3$); [lit.[4f] $[\alpha]_D^{22}$ +19° (c 0.47 $CHCl_3$)]; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.79 (t, J = 7 Hz, 3 H), 1.00 (t, J = 8 Hz, 3 H), 2.10 (s, 3 H), 3.62 (s, 3 H), 3.79 (s, 3 H), 3.82 (s, 3 H), 5.29 (d, J = 8 Hz, 1 H), 5.45 (s, 1 H), 5.51 (m, 1 H), 5.83 (m, 1 H), 6.12 (s, 1 H), 6.56 (s, 1 H), 7.1 (m, 3 H), 7.60 (d, J = 7 Hz, 1 H), 8.04 (s, 1 H), 9.72 (br s, 1 H); HREIMS calcd for $C_{61}H_{56}N_4O_8$ 792.4100, found 792.4095 (b), 761, 733, 669, 633, 509, 446, 336, 335; CD (EtOH, λ_{max}) 305 nm ($\Delta\epsilon$ +6.7), 258 nm ($\Delta\epsilon$ +14.0), 227 nm ($\Delta\epsilon$ +23.0); UV (EtOH, λ_{max}) 222 (ϵ 45300), 261 (ϵ 18600), 288 (ϵ 14700), 295 nm (ϵ 13700); IR ($CHCl_3$, cm^{-1}) 3460, 1740, 1620. The solvents from the first fractions of the above chromatography were removed in vacuo, and the residue was purified by a second flash chromatography (95% CH_2Cl_2/MeOH). The initial fractions contained unreacted (−)-vindoline (20 mg, 0.044 mmol), and subsequent fractions provided (−)-anhydrovincovaline (**17a**) (20 mg, 0.0252 mmol) as a white powder in 54% yield based on (−)-catharanthine: mp 196–199 °C; $[\alpha]_D^{22}$ −104° (c 0.70 EtOH); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.36 (t, J = 7 Hz, 3 H), 1.01 (t, J = 7 Hz, 3 H), 2.06 (s, 3 H), 2.74 (s, 3 H), 3.56 (s, 3 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 5.21 (d, J = 8 Hz, 1 H), 5.46 (s, 1 H), 5.55 (m, 1 H), 5.78 (dd, J = 6, 4 Hz, 1 H), 6.15 (s, 1 H), 6.71 (br s, 1 H), 7.1 (m, 1 H), 7.2 (m, 2 H), 7.51 (d, J = 8 Hz, 1 H), 8.06 (s, 1 H), 9. 58 (br s, 1 H); HREIMS calcd for $C_{46}H_{56}N_4O_8$ 792.4100, found 792.4095, 733, 669, 633, 446, 352, 336, 335, 282, 231 (b); CD (EtOH, λ_{max}) 305 nm ($\Delta\epsilon$ −5), 284 nm ($\Delta\epsilon$ −3), 258 nm ($\Delta\epsilon$ +3), 225 nm ($\Delta\epsilon$ −20); UV (EtOH, λ_{max}) 213 nm (ϵ 51500), 256 nm (ϵ 15800), 289 nm (ϵ 12300), 296 nm (ϵ 12300); IR ($CHCl_3$, cm^{-1}) 3460, 1745, 1628, 1620.

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