Pergamon

Tetrahedron 54 (1998) 6259–6292

TETRAHEDRON

Synthesis and Oxidative Fragmentation of Catharanthine Analogs. Comparison to the Fragmentation - Coupling of Catharanthine and Vindoline

Richard J. Sundberg,* Jian Hong, Stanton Q. Smith and Michal Sabat

University of Virginia, Department of Chemistry, Charlottesville, VA 22901

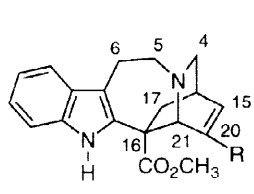
Ibro Tabakovic

Department of Chemistry, University of Minnesota, Minneapolis, MN 55455

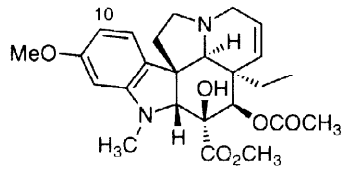
Received 25 September 1997; revised 5 February 1998; accepted 27 March 1998

Abstract: Two new analogs of catharanthine have been synthesized in racemic form. They differ from catharanthine in the fusion of the indole ring to the non-aromatic portion of the *iboga* skeleton, with the [2,3] fusion present in catharanthine being replaced by [2,1] and [3,2] fusions. The corresponding deethyl analogs were also prepared and methodological improvements were applied to an existing synthesis of deethylcatharanthine and a formal synthesis of racemic catharanthine. The reactivity of the catharanthine analogs toward coupling with vindoline was examined. Coupling was attempted by both the amine oxide fragmentation (Potier) and Fe^{3+} methods. Under Potier conditions the [2,1] fused analogs give low yields of coupling products in which vindoline is attached to the 3-position of the indole ring. The [3,2] isomers undergo fragmentation of the C16-C21 bond, as observed for catharanthine, but no coupling to vindoline occurs. The reactivity, oxidation potentials and conformation of the analogs are compared with catharanthine, deethylcatharanthine and N-methylcatharanthine.

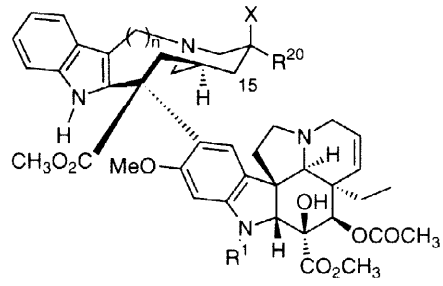
The dimeric *vinca* alkaloids vincristine (VCR) and vinblastine (VLB), originally reported in 1960, are of major significance in cancer chemotherapy.[1] Early successes in treatment of leukemia and Hodgkin's disease have been followed by development of many combination therapies which include VCR or VLB as one of the agents.[2] More recently the semi-synthetic analog vinorelbine has been introduced into clinical use.[3]



R = Et Catharanthine



Vindoline



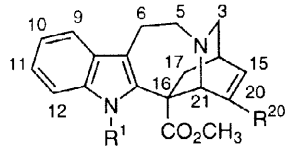
R^1 = Me, R^{20} = Et, X = (=C15), n = 2 Anhydrovinblastine (AVLB)
R^1 = Me, R^{20} = Et, X = OH, n = 2 Vinblastine (VLB)
R^1 = CHO, R^{20} = Et, X = OH, n = 2 Vincristine (VCR)
R^1 = Me, R^{20} = Et, X = (=C15), n = 1 Vinorelbine

0040-4020/98/$19.00
PII: S0040-4020(98)00289-0

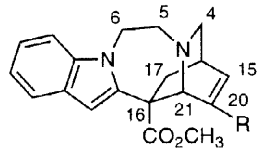
The importance of the dimeric *vinca* alkaloids has resulted in numerous studies of the synthesis and biological evaluation of analogs. The methods explored for synthesis of analogs include modification of the naturally occurring dimer,[4] construction of dimers by coupling modified versions of the monomeric precursors catharanthine or vindoline,[5] and construction of the catharanthine-derived portion by total synthesis.[6]

I. Synthesis of Catharanthine Analogs

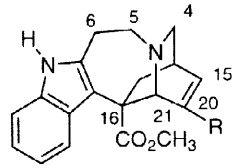
In previous work we reported the synthesis of 6-*nor*-[7a] and 5,6-*homo*-20-deethylcatharanthine,[7b] as well as related 15-oxo derivatives.[7c,7d] In this paper we report the synthesis of four new catharanthine analogs having alternative fusions of the indole ring to the isoquinuclidine portion of the *iboga* skeleton in which the natural indole [2,3] fusion is replaced by [2,1] (**8b**) and [3,2] fusions (**18b**). The racemic C20-deethyl analogs were also synthesized (**8a**, **18a**). Improvements in our earlier synthesis of (±)-20-deethylcatharanthine[8] (**10a**) are also reported. Those improvements were applied to a formal synthesis of (±)-catharanthine (**10b**).



R^1 = H, R^{20} = H **10a**
R^1 = H, R^{20} = Et **10b**
R^1 = Me, R^{20} = Et **10c**



[2, 1] fusion
R = H **8a**
R = Et **8b**



[3, 2] fusion
R = H **18a**
R = Et **18b**

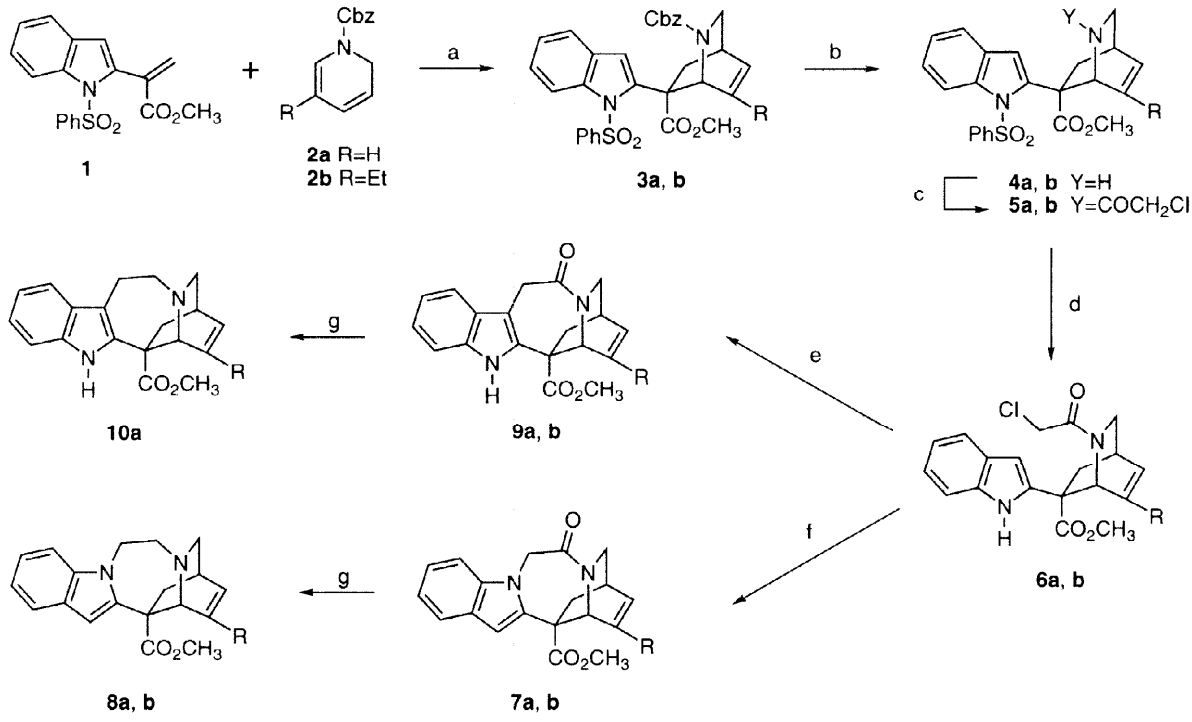
Compound **6a**, a key intermediate in the synthesis of 20-deethylcatharanthine (**10a**), is also a potential precursor of the [2,1]-isomer **8a**. In the synthesis of **10a**, photocyclization of **6a** results in closure of the C6-C7 bond to give **9a**.[8] It seemed likely that a base-catalyzed reaction would lead to C6-N1 cyclization by the indole anion and formation of the isomer **7a**. The starting material **3a** is available from the Diels-Alder reaction of methyl 2-(1-phenylsulfonylindol-2-yl)propenoate (**1**) and 1-benzyloxycarbonyl-1,2-dihydropyridine (**2a**). An improved N4-deprotection of **3a** was developed using trimethylsilyl iodide for cleavage. Chloroacetylation to give **5a** was then carried out using chloroacetic anhydride.

A selective removal of the phenylsulfonyl protecting group without affecting the chloroacetyl group was achieved by use of the photochemical desulfonylation conditions developed by Yonemitsu and coworkers.[9] Photolysis through Vycor with 1,5-dimethoxynaphthalene and ascorbic acid as reductant resulted in a 66% yield of **6a** without competing photolysis of the chloroacetyl group. Intermediate **6a** was then cyclized to **7a** in 83% yield by treatment with NaH in THF. If, instead, **6a** was subjected to photolysis through Vycor in methanol, 5-

oxo-20-deethylcatharathine **9a**, a precursor of **10a**, was obtained in 45% yield.

The same approach was applied to the Diels-Alder adduct **3b** obtained from **1** and **2b**. Racemic 5-oxo-catharanthine (**9b**) was obtained. The material had spectroscopic properties identical to those reported by Szantay who obtained **9b** by an alternate route.[10] This constitutes a formal synthesis of (±)-catharanthine (**10b**) since Szantay has previously converted **9b** to (±)-**10b**.[10] Treatment of **6b** with NaH in THF led to the N1-C6 cyclization product **7b** in 81% yield.

Scheme 1.



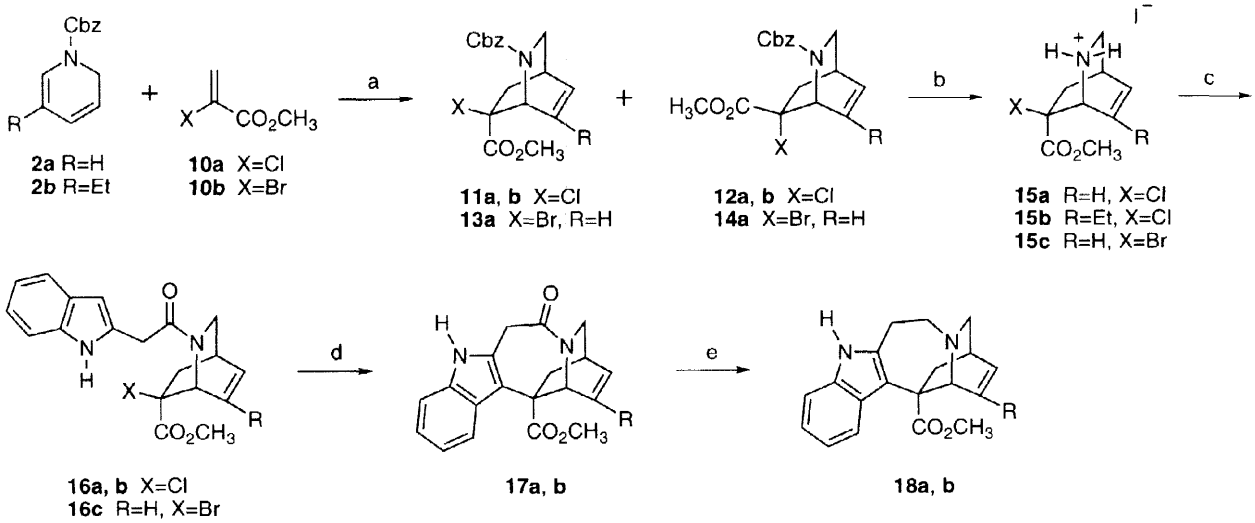
Conditions. a) 100°C, 60h. b) TMSI, CH_2Cl_2. c) chloroacetic anhydride, DMAP, CH_2Cl_2.
d) hv, pyrex filter, 1,5-dimethoxynaphthalene, ascorbic acid. e) hv, vycor filter. f) NaH, THF, rt.
g) $NaBH_4$, BF_3-OEt_2, THF.

Our previous method for reduction of 5-oxocatharanthine analogs involved reduction of the corresponding *S*-methyl thioimmonium salts.[8] However, Szantay and coworkers used *in situ* generation of diborane for this reduction, despite the presence of the C15-C20 double bond.[11] Application of their method to **9a** gave excellent conversion to **10a**. These improvements reduce the number of steps from **3a** to 20-deethylcatharanthine from 7 to 4 and improve the yield to 24% compared to 18% for the published synthesis.

Use of the *in situ* diborane conditions for reduction of the [2,1]-analog **7a** was much more problematic. The reaction was highly sensitive to reaction temperature and the solvent used for extractive work up. The best yield achieved was 40%. Among the key variables were reaction temperature (0°C) and extraction solvent (CH_2Cl_2, EtOAc >> $CHCl_3$). Although the competing processes have not been identified, boronation at the open indole ring position may be the origin of the problem.[12] The reduction completed the synthesis of **8a** in overall 8% yield from **3a**. A parallel series of reactions starting with **3b** led to **8b** in overall 14% yield from **3b**.

An attempt to develop a parallel synthesis of the [3,2]-isomer **18a** using methyl 2-(1-phenylsulfonylindol-3-yl) propenoate failed because this substance was very prone to dimerization.[13] No Diels-Alder adduct could be isolated after attempted reaction with the dihydropyridine **2a**. However an adaptation of a route to catharanthine used by Szantay[10] and Raucher[14] provided access to **18a** and **18b**. Methyl 2-chloropropenoate is known to react with **2b** to give a mixture of *exo*- and *endo* Diels-Alder adducts **11a** and **12a**.[10,11,14] These adducts were separated and deprotected with TMSI. Coupling of **11a** with indole-2-acetic acid using DCCI then gave **16a**. As compared with Szantay's and Raucher's photocyclizations which occur at the 2-position of the indole ring, the photocyclization of **16a** involves the 3-position of the indole ring. The direct photolysis of **16a** proceeds in 20-25% yield which is comparable to Szantay's results (16% yield) for the indole-3-acetic acid amide.[11] A similar reaction sequence converted **11b** to **16b**. It was photocyclized to **17b** in 23% yield. The bromo analog **16c** was also prepared but it afforded no improvement in yield. The photocyclization products **17a** and **17b** were reduced using the *in situ* borane procedure in good yield to **18a** and **18b**, respectively.

Scheme 2.



Conditions. a) toluene, 80°C. b) TMSI, rt. c) 2-indolylacetic acid, DCC, CH_2Cl_2, rt, overnight. d) hv, Vycor filter, sodium carbonate, methanol-water, 5h. e) $NaBH_4$, BF_3*OEt_2, THF.

II. Reactivity Under Coupling Conditions

Several methods are now available for coupling of catharanthine with vindoline[15-19] The most prominent are the fragmentation of catharanthine-N-oxide by trifluoroacetic anhydride (TFAA)[15] (Potier fragmentation) and Fe^{3+} oxidative fragmentation.[16] The amine oxide fragmentation has proven to be quite limited in its structural scope, however. The following structural modifications all result in failure of coupling under these conditions: (1) saturation of the C15-C20 double bond;[16] (2) deletion of C6 to give *nor*-catharanthine;[20] (3) addition of an extra carbon in the tryptamine bridge to give C5-C6-*homo*-catharanthine.[21] No catharanthine analogs have been used in the Fe^{3+} coupling procedure. We have now studied the reactivity of the catharanthine analogs **8a, 8b, 18a and 18b** with vindoline under both the Potier and Fe^{3+} coupling procedures.

A. [2,1]-Analogs 8a and 8b

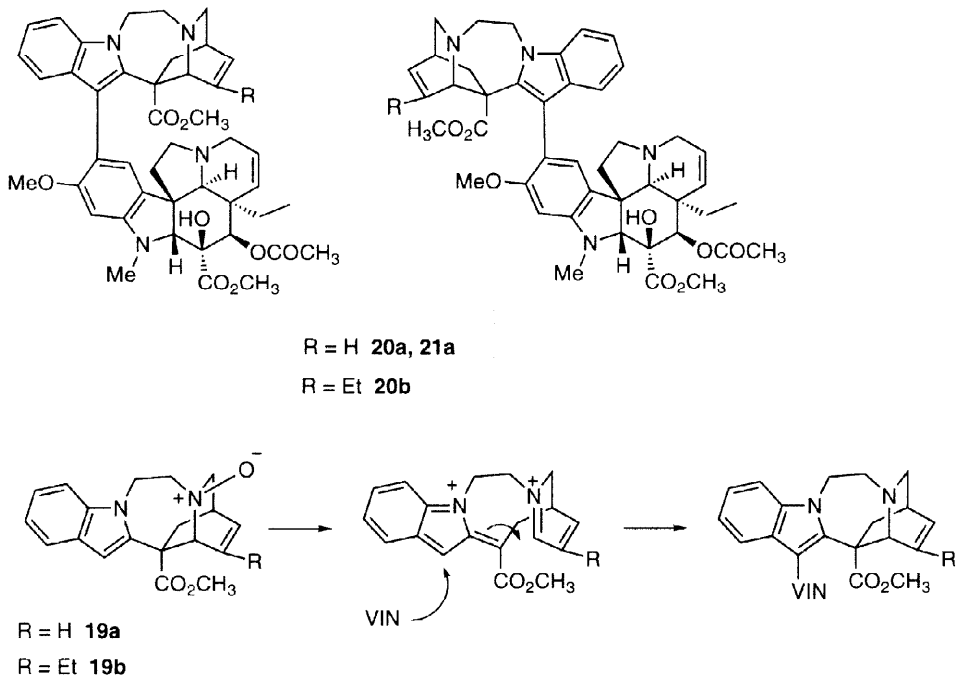
Several groups have reported Fe^{3+}-mediated coupling of catharanthine and vindoline.[16] We used the conditions of Szantay et al. which use 6-20 equivalents of $FeCl_3$ in aqueous 0.05 M glycine solution.[16d] The conditions used for the amine oxide fragmentation were those developed by Potier *et. al.* and involve low temperature treatment of the amine oxide with TFAA.[15a] In both procedures, the coupled product anhydrovinblastine (AVLB) is isolated after $NaBH_4$ reduction of a dihydropyridinium intermediate.

When [2,1]-analogs **8a** and **8b** were subjected to Fe^{3+} conditions, both in the presence and absence of vindoline, the reactants were recovered unchanged. The Fe^{3+}-glycine system evidently is not a sufficiently strong oxidant to oxidize the [2,1]-isomers, which have a somewhat higher oxidation potential than either the [2,3] and [3,2] analogs, *vide infra.*

Conversion of **8a** to its N-oxide (**19a**) and reaction with vindoline under the Potier conditions resulted in a product mixture containing mainly unreacted vindoline and a small amount (10-15% each) of two apparent coupling products, as indicated by appearance of two new sets of singlets at 6.2 and 6.6 ppm and at 6.1 and 6.9 ppm, suggestive of C10-substitution on vindoline. Essentially all of the **19a** reacted. However, no peaks attributable to products derived from **19a**, except those assigned to the coupled products, were evident in the crude product. Purification of the reaction mixture by flash chromatography followed by radial chromatography lead to the isolation (2-3% yield each) of two substances, each with apparent molecular ions at 763 amu which showed two singlets in the NMR at 6.2 and 6.6 and 6.1 and 6.9, respectively, confirming substitution at C10 of

vindoline. The observed $M^{+\cdot}$ is two amu less than anticipated for a fragmentation-coupling-reduction analogous to the formation of AVLB from catharanthine and vindoline. Precedented coupling products of MW 763 might include elimination followed by addition of vindoline at C3 or C5[20] or C5-C6 fragmentation followed by addition of vindoline at C5 and N1-C6 cyclization.[15a,22] The absence of an ^{1}H-NMR signal attributable to a indole-3H excluded such structures. The presence of peaks characteristic of an intact isoquinuclidine structure with C15-C20 unsaturation, including the C21 (4.13 ppm), C17 (1.80) protons, and consistent COSY couplings indicated the "dimers" were the diastereomers **20a** and **21a**. The formation of structures **20a** and **21a** can be rationalized by a C16-C21 fragmentation analogous to that observed for catharanthine but with capture of vindoline at C7 rather than C16. Reformation of the C16-C21 bond could occur through a Mannich-type addition. (Scheme 3)

Scheme-3



In an effort to determine the fate of the remainder of the **19a** it was subjected to Potier conditions in the absence of vindoline, followed by the $NaBH_4$ reductive work-up. A very good recovery of **8a** was obtained. A similar experiment was also done using $NaBD_4$. The recovered **8a** contained no deuterium. These results indicate that no fragmentation of **19a** occurred in the absence of vindoline and that it was simply reduced back to **8a** by $NaBH_4$ or $NaBD_4$. The implication of these experiments is that vindoline catalyzes or induces the fragmentation reaction, a phenomena previously observed for catharanthine-N-oxide.[23]

The results with **8b** were very similar. All of the amine oxide **19a** reacted to give a mixture containing mainly unreacted vindoline, but showing NMR peaks suggesting one or more coupling products. A dimeric material **20b** was characterized having spectral features closely analogous to one of the **20a, 21a** diastereomers. In particular, the signal for C21 proton appears at 4.2 ppm as a singlet, consistent with the assignment to the bridgehead position.

B. [3,2]-Analogs 18a and 18b

The principal product from reaction of **18b** under Fe^{3+} coupling conditions with $NaBH_4$ work-up was the allylic alcohol *E*-**24b**. The structure assignment was based on ^{1}H-NMR, COSY and ^{13}C-NMR spectra. The ^{1}H-NMR data are given in Table 1. Nearly all of the vindoline was recovered unchanged. When the $NaBH_4$ reduction step was eliminated, the crude product mixture contained the aldehyde *Z*-**23b** and its *E*-isomer in about 40% total yield. The same aldehydes were formed in 30% yield when vindoline was omitted from the reaction mixture. Under the Potier conditions, **18b** gave a 1.2:1 mixture of aldehydes *E*-**23b** and *Z*-**23b** in about 45% yield. The fragmentation proceeded with or without vindoline in the reaction mixture.

Similarly, **18a** underwent oxidative fragmentation by Fe^{3+} but no coupling product was observed. The aldehyde **23a** was obtained as a 10:1 *E*:*Z* mixture in about 35% yield. When a reductive work-up with $NaBH_4$ was done, the allylic alcohol *E*-**24a** was isolated. The same aldehydes were observed, along with some unreacted **18a** when vindoline was omitted from the reaction mixture. Reaction of **18a** and vindoline under Potier conditions gave no indication of a coupling product. Most of the vindoline remained unchanged but no product due to the **18a** could be isolated.[24]

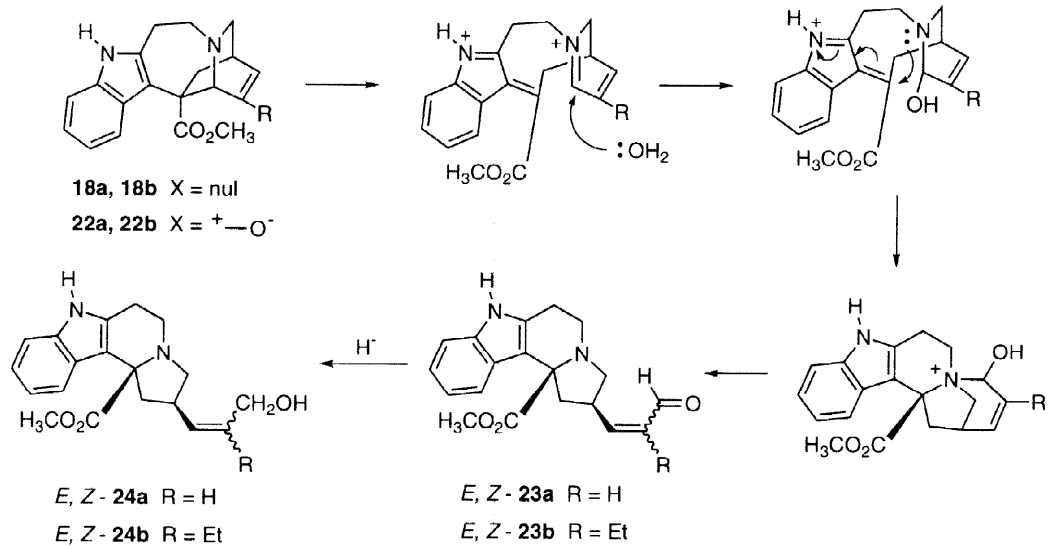
The results from attempted couplings of **18a** and **18b** are summarized in Table 2. While the details of the individual reactions varied, the common pattern is that C16-C21 fragmentation occurs, but there is no evidence that the fragmentation product is trapped by vindoline. Instead the dominant process is N4-C16 bond formation, followed by ring opening between N4 and C21 leading to aldehydes **23a** and **23b** (Scheme 4).

C. Catharanthine Derivatives.

For comparison with the [2,1] and [3,2] analogs we also examined the reaction of catharanthine with Fe^{3+} in the presence and absence of vindoline. Anhydrovinblastine (AVLB) was obtained in good yield, in accord with previous work.[16] Surprisingly, we found that almost no reaction occurred when vindoline was absent from the reaction mixture. Under conditions where >90% fragmentation-coupling occurs in the presence of vindoline,

< 10% conversion of catharanthine occurred. Only trace amounts of an unidentified possible oxidation product were visible in the NMR spectrum. The implication is that vindoline participates in the rate-determining step for Fe^{3+} oxidation of catharanthine. To the best of our knowledge, this is a new observation.[25]

Scheme 4



20-Deethylcatharanthine (**10a**) has previously been coupled with vindoline under Potier conditions.[26] Two diastereomeric adducts **25a** and **26a** were isolated in 15% yield each. **10a** has not previously been coupled with vindoline under Fe^{3+} conditions. The reaction provided the same two adducts obtained from the Potier coupling in about 30% yield each. The adducts had the features expected for deethyl analogs of AVLB and the ^1H NMR chemical shifts are in agreement with those reported earlier.[26] As with catharanthine, the omission of vindoline significantly retarded oxidation. Only about 20% of conversion occurred under the standard conditions, with the remainder of the **10a** being recovered (Scheme 5).

N-Methylcatharanthine (**10c**) has previously been shown to undergo oxidative fragmentation under Potier conditions, although coupling with vindoline has not been established.[23] In the Fe^{3+} system, **10c** was nearly completely converted in the presence of vindoline but no evidence of coupling was found. Most of the vindoline was recovered, but no oxidation products derived from **10c** could be identified. In the absence of vindoline, **10c** was recovered unchanged. Thus each of the catharanthine analogs is considerably less reactive under the Fe^{3+} conditions when vindoline is not included.

Table 1. NMR Data for 23a, 23b, 24a, 24b[a]

	1-NH	$3CH_2$, $5CH_2$, $6CH_2$, 14CH, $17CH_2$	9CH, 10CH, 11CH, 12CH	15CH	R	X	CO_2CH_3
E-23a	7.96s	3.6-3.7m; 3.35 dd (J = 14.0, 6.0); 3.1-3.2 m (2H); 3.07 ddd (J = 17.0), 11.5, 5.5); 2.8-2.95 m (2H); 2.68 m 2.57 bd	7.67 d (J = 7.8); 7.31 d (J = 7.8); 7.21 t (J = 7.8); 7.13 t (J = 7.8)	6.94 dd (J = 15.5, 8.0)	6.50 dd (J = 15.5, 7.5)	9.5 d J = 7.5	3.73s (3H)
E-24a	8.02s	3.8-4.0 m (2H); 3.40 m, 3.02-3.2 m (3H); 2.75 dd (J = 11.0, 7.0); 2.4-2.7 m (2H)	7.78 d (J = 7.8); 7.35 d (J = 7.8); 7.19 t (J = 7.8); 7.13 t (J = 7.8)	5.78 dd (J = 16.5, 8.0)	5.61 dt (J = 16.5, 6.5, 6.5)	4.08 m (2H)	3.75s (3H)
E-23b	7.98s	3.5-3.8 m (2H); 3.36 dd (J = 14.0, 5.15); 3.0-3.3 m (3H); 2.90 dd (J = 12.5, 8.0); 2.58 m (2h)	7.66 d (J = 7.8); 7.34 d (J = 7.8); 7.18 t (J = 7.8); 7.17 t (J = 7.8)	6.57 d (J = 10.3)	2.19 q (2H, J = 7.5); 0.98 t (3H, J = 7.5)	9.90s	3.72s (3H)
Z-23b	7.94s	3.6-3.8 m; 3.4 m; 3.0-3.3 m (4H); 2.8-3.0 m; 2.6 m (2H)	7.67d (J = 7.8); 7.35 d (J = 7.8); 7.22 t (J = 7.8); 7.14 t (J = 7.8)	6.63 d (J = 8.8)	2.10 q (2H, J = 7.5); 1.00 (3H, J = 7.5)	9.93s	373s (3H)
E-24b	7.93s	3.55-3.65 m (2H); 3.31 dd (J = 14.0, 5.4); 2.98-3.12 m (3H); 2.90 m; 2.76 dd (J = 12.1, 7.2); 2.50 dd (J = 16.5, 4.3); 2.39 dd (J = 12.4, 8.1)	7.68 d (J = 7.8); 7.35 d (J = 7.8); 7.18 t (J = 7.8); 7.12 t (J = 7.8)	5.40 d	2.10 q (2H, J = 7.5); 1.02 t (3H, J = 7.5)	3.98 q (J_{gem} = 12)	3.70s (3H)

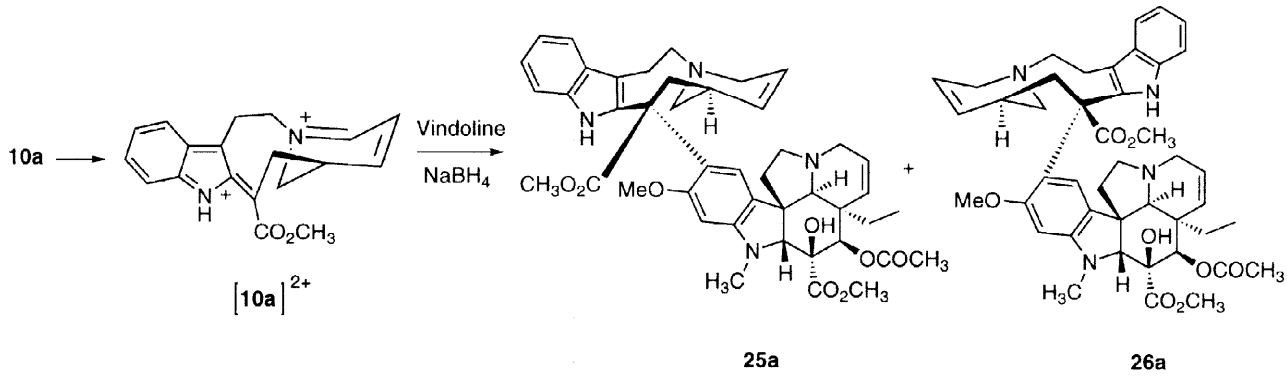
(a) 300 Mhz in $CDCl_3$. Unless indicated otherwise, all peaks represent a single (1H) proton. Coupling constants are ± 0.3 Hz.

Table 2 Summary of Results

	Ferric Chloride (Product Ratios from NMR)[a]					Potier-Polonovsky (Product Ratios from NMR)[a]			
	Reactants		Recovered Reactants		Products	Reactants	Recovered Reactants		Products
Analog	VIN	Fe^{3+} (eq)	VIN	Analog		VIN	VIN	Analog	
10a	1	10	30%	10%	**25a** (30%) **26a** (30%)	1.1	0%	0%	**25a** (16%) **26a** (16%)[Ref. 26]
	0	10	___	80%					
10b	1	8	20%	20%	AVLB (62%)	1.1	0%	0%	AVLB (50-60%)[Ref.15a]
	0	8	___	90%	___				
10c	1	16	100%	<10%	unidentified	experiment not done			
	0	16	___	90%					
18a	1	7	100%	40%	*Z*-**23a** (3%) *E*-**23a** (32%)	1.1	90%	0%	unidentified
	0	11	___	90%	*E*-**24a**[b]	0	___	0%	unidentified
	0	25	___	50%	*E*-**23a** (30%)				
18b	1	30	80%	0	*E*-**24b** (40%)[b]	1.1	90%	0%	unidentified
	0	6	___	90%	*E*-**23b** (5%)	0	___	0%	*Z*-**23b** (30%)
	0	27	___	60%	*Z*-**23b** (5%) *E*-**23b** (25%)				
8a	1	6-22	100%	100%	no reaction	1.1	80%	0%	**20a** (10%) **21a** (10%)
	0	6-30	___	100%	no reaction	0	___	75%	unidentified
8b	1	10	100%	100%	no reaction	1.1	70%	0%	**20b** (12%) **21b** (12%)
	0	9	___	100%	no reaction	experiment not done			

a. Product yields were estimated from the mass balance of the crude product and the ratio of characteristic peaks in the NMR spectrum. Relative accuracy is estimated to be ±20%. There was some variation in extent of conversion from run to run. b. Reductive workup. c. See footnote 23.

Scheme-5



In order to explore this observation further, an additional experiment was done in which racemic **10a** was present in 2:1 excess to vindoline under Fe^{3+} coupling conditions. The reaction proceeded normally and all of the vindoline reacted. The NMR of the recovered **10a** was examined with Eu(hfc), shift reagent (0.3-0.5 equiv.) under conditions where excellent separation of the NH resonances of the **10a** enantiomers could be observed. Within the accuracy of the measurement (±10%), there was no selectivity with respect to the enantiomers. This experiment indicates that, whatever the nature of the interaction that promotes reaction in the presence of vindoline, it is not highly enantioselective for the **10a** enantiomers. It should be noted that the Potier coupling of (±)-**10a**[26] and (±)-catharanthine[27] also are not very stereoselective

III. Electrochemistry

The electrochemistry of catharanthine has been previously reported[18] and the voltammograms of **10a**, **10b**, **10c**, **8a**, **8b**, **18a**, **18b**, and vindoline were obtained in CH_3CN-0.1 M $LiClO_4$ solution at glassy carbon electrode. The voltammetry of **10a** was studied in some detail. A close analogy with the results for catharanthine was noted.

The cyclic voltammogram of **10a** presented in Figure 1a shows two anodic peaks at 0.52 and 1.2 V vs. SCE, respectively. The first wave corresponds to the oxidation of **10a** and the second wave is due to $\mathbf{10aH}^+$ from the protonation of the parent molecule by protons liberated in the electrode reaction along the first wave. The ratio of the peak currents between the first and second wave was increased by increasing of the sweep rate, v. The average value of the transfer coefficient obtained from the peak widths (Ep-Ep/2) for the first wave at eight sweep rates fits well for α=0.60 and n=1. When the cyclic voltammogram was run in the presence of 2,6-lutidine, the current of the first peak increased (Fig. 1b). The height of the peak current corresponds to a two electron oxidation, assuming that the value of the diffusion coefficient for **10a** is the same as previously

determined for catharanthine (D = 1.4x10-5 cm^2/s).[18] The wave obtained in the presence of 2,6-lutidine is broader and the average value of the transfer coefficient obtained from the peak widths for **10a** (α=0.52) is similar to catharanthine (α=0.51) under the same experimental conditions. This result indicates that 2,6-lutidine provides an additional driving force for C16-C21 fragmentation of the intermediate radical cation of **10a**.[27]

The coulometry at controlled potential of **10a** was performed at a platinum gauze electrode in CH_3CN-0.1 M $LiClO_4$ solution containing 2,6-lutidine. Cyclic voltammograms under constant conditions were obtained as a function of the charge passed. The results show that under controlled potential electrolysis, the oxidation wave at 0.51 V vs. SCE decreases at a rate corresponding to the consumption of 2 F/mol. At the end of the electrolysis a new peak at 0.65 V vs. SCE appeared, presumably corresponding to the oxidation product formed. The n value calculated from the cyclic voltammograms of **10a** (see Experimental) as a function of the sweep rates, v, was found to increase by increasing log v. In the presence of 2,6-lutidine, the voltammograms of **10a** showed n=2 (Fig. 1). The increase of n values with the sweep rates for **10a** without the presence of 2,6-lutidine can be explained by the equations (1-3).

$$\mathbf{10a} - 2e \rightarrow [\mathbf{10a}]^{+2} \quad (1)$$

$$[\mathbf{10a}]^{+2} + H_2O \rightleftharpoons [\mathbf{10a\text{-}OH_2}]^{+2} \quad (2)$$

$$[\mathbf{10a\text{-}OH_2}]^{+2} + \mathbf{10a} \rightarrow [\mathbf{10a\text{-}OH}]^{+} + [\mathbf{10aH}]^{+} \quad (3)$$

A two electron oxidative fragmentation of **10a** gives dication, $[\mathbf{10a}]^{2+}$ (eq. 1) which is attacked by water, presumably at the position C21, giving $[\mathbf{10a\text{-}OH_2}]^{2+}$ (eq. 2). A diffusing molecule of **10a** acts as a base deprotonating $[\mathbf{10a\text{-}OH_2}]^{2+}$ (eq. 3) and therefore lowering n value from n=2 to n=1. This reaction scheme can be considered as a self-protonation for which a detailed kinetic studies were reported.[29] The theoretical treatment of self-protonation reaction demonstrates that the apparent number of electrons n is particularly affected by the variation of the rate of the following chemical reaction and sweep rate. At slower anodic sweep rates there is enough time for the following chemical reactions (eq. 2 and 3) to occur which results with the lower n values. At higher sweep rates, n gradually increases because the chemical reactions do not compete with diffusion.

The cyclic voltammograms of the other compounds, listed in Table 1, are also characterized by the same basic patterns. The relative ease of removing an electron from the tertiary amine moiety varies substantially among these compounds. The range for the peak potentials, E_p, varies from 0.50 to 0.64 V vs. SCE for catharanthine, **10a** and the [3,2]-derivatives. The [2,1]-analogs **18a** and **18b** are harder to oxidize and showed

E_p values of 0.83 and 0.77 V vs. SCE, respectively. All experimentally determined values for the transfer coefficient, α, fell in the range 0.54 to 0.68. The irreversibility is the result of the slow electron transfer. Oxidation at N4 is accompanied with the changing of hybridization of the amine moiety from sp^3 to sp^2 of the resulting radical cation. Strain energy distorts the planar configuration thereby increasing the free energy for electron transfer. The electrochemistry of vindoline was studied previously[30] and results in Table 3 are also given for the purpose of comparison.

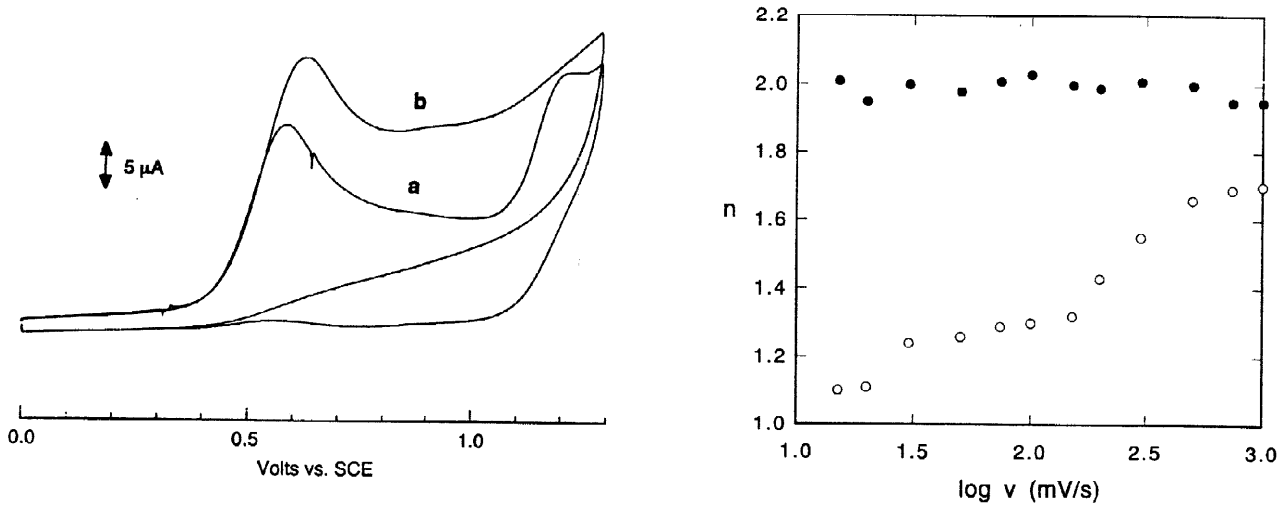
The shape of the voltammograms for all compounds listed in Table 3 in the presence of vindoline were studied in acetonitrile solution. Three types of voltammograms, i.e. A, B, and C in Figure 2, were obtained. Type A voltammograms, exemplified by that for **10a** with and without vindoline are shown in Figure 2a. The peak potential of **10a** in the presence of vindoline was shifted about 30 mV cathodically indicating that the overall rate of the fragmentation/coupling reaction is enhanced by the presence of vindoline, which is consistent with previous chemical[23] and electrochemical[18] studies on catharanthine. The cyclic voltammogram for **18a** (Fig. 2b) represents type B in which there is no essential change of the oxidation wave with or without vindoline. Type C voltammograms (Fig. 2c), as found for **8b** in the presence of vindoline, shows increase of the peak current which is result of the overlapping waves for **8b** and vindoline due to their close oxidation potentials.

Table 3. Oxidation peak potentials and shapes of cyclic voltammograms

Compound	E_p1[a] (V vs. SCE)	E_p2 (V vs. SCE)	αn	Shape of Cv[b]
10a	0.51	1.17	0.60	A
10b	0.50	1.15	0.59	A
10c	0.64	1.18	0.68	B
18a	0.56	1.32	0.56	B
18b	0.52	1.24	0.62	B
8a	0.83	1.34	0.54	C
8b	0.77	1.26	0.54	C
Vindoline	0.76	0.92	0.68	-

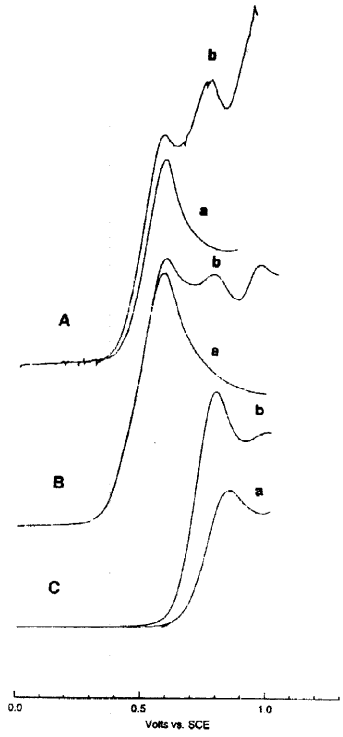
a) Sweep rate: 50 mV/s; GCE (A = 0.05 cm^2); CH_3CN- 0.1 M $LiClO_4$.
b) In the presence of vindoline.

Figure 1



Left: **Cyclic voltammograms in CH_3CN-0.1 M $LiClO_4$; GCE; v=75 mV/s; (a) 10a (1 mM); (b) plus 2,6-lutidine (4 mM); Right: Sweep rate dependance of the apparent number of electrons n for oxidation of 10a (1 mM) o: plus 2,6-lutidine (4 mM).**

Figure 2



Cyclic voltammograms in CH_3CN-0.1 M $LiClO_4$; GCE; v=50 mV/s; A (a) DECATH (1 mM), (b) plus VIND (1 mM); B (a) *inv*-DECATH (3.8 mM), (b) plus VIND (1.3 mM); C (a) *iso*-CATH (1.78 mM), (b) plus VIND (1.4 mM).

IV. Conformational Analysis

Since fragmentation of the C16-C21 bond is expected to involve participation by the indole ring, the orientation of that bond with respect to the indole ring is presumably a crucial structural factor. Molecular models suggest two potential conformations with values of the dihedral angle θ between the plane of the indole ring and the C16-C21 bond of about 0° and 60°, corresponding to boat-like and chair-like conformations of the seven-membered C-ring. To pursue this point, minimizations using the MacroModel routine were done for **10a**, **10c**, **8a** and **18a**. The dihedral angles for the minima were 33.4°, 12.2°, 39.4° and 32.8°, respectively. Thus while it appears that interaction of the N-methyl group with the C16 ester substituent in **10c** favors a boat-like conformation of the C-ring, the other analogs adopt conformations which are very similar to one another, suggesting that reactivity differences among the analogs must be primarily electronic in origin.

Discussion

Our results on coupling of catharanthine and its deethyl analog **10a** are consistent with prior studies and extend the information available on Fe^{3+}-mediated coupling. **10a** is coupled by Fe^{3+} but there is no evidence of significant enantioselectivity, consistent with the prior results of Potier coupling.[26,27] The most significant new result, which pertains to catharanthine, **10a**, and **10c** is that the reaction of the catharanthine analogs with Fe^{3+} is significantly catalyzed or induced by vindoline.

The [2,1]-analogs were unreactive toward Fe^{3+}, a result which is consistent with their higher oxidation potential. Reaction did occur under Potier conditions. However trapping by vindoline was inefficient and coupling occurs at C7 rather than C16 (*iboga* numbering). As has previously been observed with catharanthine,[23] the fragmentation reaction of **19a** appears to be catalyzed or induced by vindoline. When vindoline was omitted from Potier reactions, the only product found after reductive work up was **8a**. Furthermore, no deuterium was incorporated when $NaBD_4$ was used for reductive work-up. This excludes a C3-N4 or C5-N4 elimination followed by reduction as the source of the recovered **8a**. Instead it appears **19a** did not react in the absence of vindoline and was simply reduced to **8a** on workup.

The [3,2]-analogs underwent C16-C21 fragmentation under both Fe^{3+} and Potier conditions. The oxidation products **23a** and **23b** can be isolated in fair yield from the Fe^{3+} oxidations, but there was no evidence of coupling with vindoline. The formation of these products can be rationalized by C16-C21 oxidative fragmentation analogous to catharanthine, followed by trapping by water (Scheme 4). Under Potier conditions, **18a** gave several unidentified products and small amounts of **23a**. The aldehyde *Z*-**23b** was the main product from **18b**

under Potier conditions. Both the Fe^{3+} and Potier reactions occurred at comparable rates in the presence and absence of vindoline. Thus the [3,2]-series appears to undergo C16-C21 fragmentation in a manner analogous to catharanthine but there is no trapping by vindoline under either the aqueous Fe^{3+} conditions or the anhydrous Potier conditions. The failure to react with vindoline may reflect both decreased reactivity at the C16 carbon and greater steric shielding by the benzenoid portion of the indole ring.

In seeking to clarify the differences between the catharanthine series and the [2,1]- and [3,2]-analogs, we considered the following structural factors. (1) Catharanthine, **10a**, **18a** and **18b** can undergo fragmentation assisted by N1-deprotonation. Because of N-alkylation, **10c**, **8a** and **8b** cannot benefit from such assistance. (2) The indole ring is a better electron donor at C3 than C2 (indole numbering). As a result the fragmentation products from **18a** and **18b** should be more stable than those from catharanthine, **10a** and **8a**, **8b**. (3) If factors (1) and (2) work together in a kinetic sense, the predicted ease of oxidative fragmentation is **18a**, **18b** >**10a**, **10b** > **8a**, **8b**. This is in qualitative agreement with the observed reactivity, particularly when it is noted that vindoline acceleration appears to be required for the [2,3]- and [2,1]-series but not the [3,2]-series.

These chemical results are in qualitative agreement with the electrochemical studies. Most notably, vindoline was found to shift the oxidation potential of catharanthine and deethylcatharanthine by 30 mV. No such shift is seen with **18a** or **18b** and the reactivity of these analogs is unaffected by the presence of vindoline under chemical conditions. The [2,1]-series is the most difficult to oxidize, both under chemical and electrochemical conditions. The fact that vindoline is oxidized at a similar potential obscures any shift it might cause in the potential of **8a**. However, vindoline does appear to accelerate Potier fragmentation of the **19a**.

We refer to the accelerating effect of vindoline on both the Fe^{3+} and Potier oxidation on catharanthine, **10a** and **10c** and on Potier oxidation of **19a** as the "vindoline effect." We have previously proposed that for Potier fragmentation of catharanthine, vindoline accelerates fragmentation simply by acting as a base to deprotonate the indole-N-H and facilitate C16-C21 fragmentation, but we noted that Potier fragmentation of **10c** was also accelerated by vindoline.[23] Since **10c** and the [2,1]-analogs are substituted at nitrogen, the deprotonation mechanism is not applicable. Furthermore, the observation of the "vindoline effect" in Fe^{3+} oxidation 0.05 M glycine solution, where solution acidity should be independent of vindoline, suggests some mechanism besides N-deprotonation must operate. The "vindoline effect" in the Fe^{3+} oxidations is the formal equivalent of a "concerted" fragmentation mechanism.[16b]

We have considered two limiting mechanistic descriptions of the "vindoline effect". One is base catalysis. We have previously cited evidence that N-deprotonation triggers C16-C21 fragmentation under Potier conditions

in the case of catharanthine.[23] The base-catalysis explanation is not applicable to **10c** or the [2,1]-series, yet acceleration of Potier fragmentation is noted for **10c** and **19a** and Fe^{3+} oxidation is also accelerated for **10c**. Acceleration might come from π-π electronic interaction through which vindoline increases the effective electron-density of the indole ring. The extreme for such a π-π interaction would be concerted electron transfer leading to coupling.

From a synthetic perspective, the salient outcome of the present work is further evidence of the extremely tight structural parameters which limit the catharanthine-vindoline coupling process. While deethylcatharanthine **10a** retains the ability to couple, albeit with somewhat reduced efficiency, under both the Fe^{3+} and Potier conditions, both the [2,1] and [3,2]-series fall outside these parameters, despite their close structural relationship to catharanthine. The other noteworthy observation is the evidence for vindoline participation in the Fe^{3+}-mediated coupling, which parallels previously noted effects in Potier oxidation and electrochemistry.

Experimental Section

Methyl 2-(benzyloxycarbonyl)-7-*exo*-(1-phenylsulfonylindol-2-yl)-2-azabicyclo[2.2.2]oct-5-ene-7-*endo* carboxylate (**3a**) A mixture of indoleacrylate **1** (6.0 g, 0.018 mol) and dihydropyridine **2a** (19.0 g, 0.088 mol) was heated in an oil bath at 100°C for 60 h under inert atmosphere. Flash chromatography (ether: CH_2Cl_2: hexane 1:1:2) gave an oil, which was crystallized from ether and hexane to give 8.29 g (84%) of **3a**, m.p. 182-184°C. ^{1}H NMR ($CDCl_3$, δ ppm, 300MHz): 7.69 (t, 1H, J = 5 Hz), 7.52 (d, 2H, J = 7.5 Hz), 7.40 (m, 2H), 7.28 (m, 2H), 7.23 (s, 2H), 7.14 (m, 2H), 6.57 (t, 1H, J = 7.5 Hz), 6.37 (t, 1H, J = 7.5 Hz), 5.46 (d, 1H, J = 6 Hz), 5.19 (d, 1H, J = 12 Hz), 3.58 (s, 3H), 2.97 - 3.06 (dd, 2H, J_1 = 13.5 Hz, J_2 = 10 Hz), 2.94 (d, 2H, J = 13.5 Hz). MW calcd. for $C_{31}H_{28}N_2O_6S$ (556.56), found MS (CI) m/z 557 ($M+1^+$).

Methyl 7-*exo*-(1-phenylsulfonylindol-2-yl)-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylate (**4a**) TMSI was prepared *in situ* from iodine (9.38 g, 0.035 mol) and hexamethyldisilane (16.4 ml, 0.084 mol). The mixture was carefully heated to 100°C until the purple color faded, and then cooled to rt. A 500 ml flask was charged with 8.0 g (0.014 mol) of carbamate **3a** in 400 ml of dry CH_2Cl_2 and cooled to 0°C. The TMSI solution was slowly added. The mixture was stirred at 0°C for one h then at rt for 30 min. When starting material was consumed, 120 ml of 0.3 M HCl in methanol was added and the mixture was stirred for one h. Then 100 ml of 10% HCl was added and stirred for 10 min. The organic solvents were removed using a rotary evaporator and the aqueous residue was extracted with ether (3 x 100 ml). The aqueous layer was then basified to pH 9 with a cold conc. NaOH solution. The mixture was extracted with EtOAc (4 x 75 ml), dried (Na_2CO_3), and concentrated to give 3.52 g (58%) of **4a** as a white foam (> 90% *endo*-carboxylate by NMR). ^{1}H NMR ($CDCl_3$, δ ppm, 300MHz): 7.73 (t, 1H, J = 4.5 Hz), 7.56 (d, 2H, J = 7.5 Hz), 7.47 (t, 1H, J = 4.5 Hz), 7.41 (t, 1H, J = 7.5 Hz), 7.31 (d, 1H, J = 7.5 Hz), 7.27 (d, 1H, J = 4.5 Hz), 7.15 (t, 2H, J_1 =

7.5 Hz, J_2 = 4.5 Hz), 7.05 (s, 1H), 6.54 (t, 1H, J = 7.5 Hz), 6.36 (t, 1H, J = 7.5 Hz), 4.26 (d, 1H, J = 7.5Hz), 3.57 (s, 3H), 2.90 (d, 1H, J = 15 Hz), 2.72 (s, 1H), 2.67 (d, 1H, J = 10.5 Hz), 2.40 (d, 1H, J = 10.5 Hz), 2.05 (d, 1H, J = 15 Hz). MW calcd. for $C_{23}H_{22}N_4O_4S$ (422.37), found MS (CI) m/z 423 ($M+1^+$).

Methyl 2-(chloroacetyl)-7-*exo*-(1-phenylsulfonylindol-2-yl)-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylate (5a) The amine **4a** (2.20 g, 5.21 mmol) was dissolved in 100 ml of dry CH_2Cl_2. This solution was cooled to 0°C and chloroacetic anhydride (2.67 g, 15.6 mmol) in 10 ml of dry CH_2Cl_2 was added followed by DMAP (191 mg, 1.56 mmol). After 20 min at 0°C, Et_3N (0.87 ml, 6.25 mmol) was added and stirring was continued at 0°C for 5 h. The reaction mixture was washed with 5% $NaHCO_3$, dried with Na_2CO_3, concentrated and subjected to flash chromatography (EtOAc:hexane 2:5) to yield 1.81 g (70%) of **5a**, m.p. 184-186°C. ^{1}H NMR ($CDCl_3$, δ ppm, 300MHz): 7.65 (t, 1H, J = 4.5 Hz), 7.50 (d, 2H, J = 7.5 Hz), 7.43 (dd, 2H, J_1 = 21 Hz, J_2 = 7.5 Hz), 7.29 (t, 2H, J_1 = 7.5 Hz, J_2 = 9 Hz), 7.15 (s, 1H), 7.12 (t, 2H, J = 7.5 Hz), 6.37 (t, 1H, J = 7.5 Hz), 5.84 (d, 1H, J = 6 Hz), 3.84 (s, 2H), 3.59 (s, 3H), 3.25 (d, 1H, J = 9 Hz), 3.10 (d, 1H, J = 15 Hz), 3.06 (d, 1H, J = 9 Hz), 3.02 (s, 1H), 2.18 (d, 1H, J = 15 Hz). MW calcd. for $C_{25}H_{23}ClN_2O_5S$ (498.91), found MS (CI) m/z 499, 501 (3 : 1) ($M+1^+$).

Methyl 2-(chloroacetyl)-7-*exo*-(indol-2-yl)-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylate (6a) Chloroacetamide **5a** (500 mg, 1.0 mmol) and 1,5-dimethoxynaphthalene (93 mg, 0.5 mmol) were dissolved in 400 ml of EtOH. This solution was then transferred into a 500 ml photolysis apparatus. Ascorbic acid (530 mg, 3.0 mmol), 50 ml EtOH and 50 ml water were added in sequence. The mixture was stirred under nitrogen and subjected to photolysis using a 450W mercury-arc Hanovia lamp in a quartz immersion well equipped with a pyrex filter sleeve for 5 h. The solvent was removed by rotary evaporation. The residue was dissolved in CH_2Cl_2, dried with K_2CO_3 and concentrated. Flash chromatography (EtOAc:hexane 2:5) gave a foam, which was crystallized with EtOAc and hexane to give **6a**, m.p. 210-211°C, lit[11] 210-211°C (273 mg, 65%). ^{1}H NMR ($CDCl_3$, δ ppm, 300MHz): 9.20 (s, 1H), 7.52 (d, 1H, J = 7.5 Hz), 7.38 (d, 1H, J = 7.5 Hz), 7.16 (t, 1H, J = 7.5 Hz), 7.06 (t, 1H, J = 7.5 Hz), 6.59 (t, 1H, J = 7.5 Hz), 6.45 (t + s, 2H, J = 7.5 Hz), 6.06 (d, 1H, J = 7.5 Hz), 3.83 (dd, 2H, J_1 = 16.5Hz, J_2 = 10.5 Hz), 3.60 (s, 3H), 3.33 (d, 1H, J = 9 Hz), 3.17 (d, 1H, J = 9 Hz), 3.04 (s, 1 H), 2.97 (d, 1H, J = 15 Hz), 2.19 (d, 1H, J = 15 Hz). MW calcd. for $C_{19}H_{19}ClN_2O_3$ (358.82), found MS (CI) m/z 359, 361 (3 : 1) ($M+1^+$).

[2,1]-Deethyllactam (7a) Sodium hydride (22 mg, 0.76 mmol, 80%/wt suspension in mineral oil) was added to a dry 25 ml flask and was washed with hexane. The NaH was then suspended in 5 ml of dry THF. Chloroacetamide **6a** (138 mg, 0.385 mmol) was dissolved in 8 ml of dry THF and added via syringe. The mixture was allowed to stir at rt for 3 h under Ar. The reaction was quenched with 1 ml of water and the THF was removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 and water. The organic phase was dried over $MgSO_4$, and the solvent was removed solvent *in vacuo* to yield 121 mg (97.5%) of crude material which was purified by flash chromatography (EtOAc:hexane = 2:1) to yield 104

mg (83%) of pure **7a**. An analytical sample was recrystallized from EtOAc and hexane, mp. 193-194°C. ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz): 7.50 (d, 1H, J = 7.5 Hz), 7.36 (d, 1H, J = 8.4 Hz), 7.24 (t, 1H, J = 8.4 Hz), 7.11 (t, 1H, J = 7.5 Hz), 6.74 (t, 1H, J = 7.2Hz), 6.38 (t, 1H, J = 6.9 Hz), 6.38 (s, 1H), 5.39 (d, 1H, J = 6.3Hz), 5.24 (d, 1H, J = 14.1Hz), 5.01 (d, 1H, J = 14.1Hz), 3.72 (dd, 1H, J_1 = 10.6Hz, J_2 = 2.5 Hz), 3.62 (s, 3H), 2.99 (dd, 1H, J_1 = 15.4 Hz, J_2 = 2.3 Hz), 2.95 (m, 2H), 1.78 (d, 1H, J = 12.3 Hz). ^{13}C NMR ($CDCl_3$) 172.54, 169.84, 139.96, 139.88, 137.62, 128.28, 127.94, 122.77, 120.90, 120.80, 110.00, 103.64, 54.74, 53.37, 51.33, 51.03, 50.19, 34.70, 31.66. MW calcd. for $C_{19}H_{18}N_2O_3$ (322.2), found MS (CI) m/z 323 ($M+1^+$). Anal. Calcd.: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.53; H, 5.73; N, 8.59.

Deethyl[2,1]-Analog (**8a**) The procedure Szantay[10,11] developed for catharanthine was used. In a 50 ml flask, lactam **7a** (20 mg, 0.062 mmol) was dissolved in 8 ml of dry THF. $NaBH_4$ (102 mg, 2.69 mmol) was added to the flask in one portion. The flask was cooled to 0°C and BF_3-OEt_2 (0.48 ml, 3.90 mmol) was syringed in over one minute. The ice bath was removed and the reaction was allowed to stir at room temperature for 3 h. The solvent was removed *in vacuo*. The residue was dissolved in 20 ml of CH_2Cl_2. Water (20 ml) was slowly added. The organic phase was dried over Na_2SO_4 and concentrated to yield 17 mg of crude material, which was subjected to flash chromatography (acetone:CH_2Cl_2 = 4:1) to yield 7 mg (37%) of pure **8a**. ^{1}H NMR ($CDCl_3$, δ ppm, 300MHz): 7.48 (d, 1H, J = 7.8 Hz), 7.27 (d, 1H, J = 6.9 Hz), 7.18 (t, 1H, J = 7.6 Hz), 7.06 (t, 1H, J = 7.5 Hz), 6.50 (t, 1H, J = 6.8 Hz), 6.38 (t, 1H, J = 6.8 Hz), 5.96 (s, 1H), 4.58 (m, 1H), 4.27 (dt, 1H, J_1 =15 Hz, J_2 = 2.7 Hz), 3.77 (s, 3H), 3.55 - 3.35 (m, 2H), 3.01 (d, 1H, J = 9.6 Hz), 2.93 - 2.80 (m, 3H), 1.79 (d, 1H, J = 12.3 Hz). ^{13}C NMR ($CDCl_3$) 174.15, 141.39, 138.39, 134.62, 134.06, 127.64, 122.05, 120.68, 120.18, 109.24, 102.38, 59.01, 57.52, 53.88, 52.79, 49.78, 41.59, 33.36, 30.74. HRMS (EI) m/z calcd. for $C_{19}H_{20}N_2O_2$ (308.1525), found 308.1534 (M^+).

Methyl 7-*exo*-(1-phenylsulfonylindol-2-yl)-2-(benzyloxycarbonyl)-6-ethyl-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylate (**3b**) A mixture of dihydropyridine **2b** (6.18 g, 25.4 mmol) and the indolyl acrylate **1** (2.5 g, 7.32 mmol) was heated without any solvent at 100°C for 60 h (under argon). The product was purified by flash column chromatography on silica gel (10% EtOAc in CH_2Cl_2) to yield 2.01 g (47%) of pure **3b** (exclusively the *exo*-indolyl adduct), as an oil. ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 7.45 - 6.95 (m, 15 H), 6.08 (dd, 1H, J_1 = 6.8 Hz, J_2 = 1.5 Hz), 5.44 - 5.01 (dd + dd', 2H, J_1 = 43.95 Hz, J_2 = 12.7 Hz), 3.56 (s, 3H), 3.10 - 2.81 (m, 5H), 2.10 - 2.00 (m, 3H), 1.08 + 1.05 (t + t', 3H, J = 7.3 Hz). MW calcd. for $C_{33}H_{32}N_2O_6S$ (584.61), found MS (CI) m/z 585 ($M+1^+$).

Methyl 7-*exo*-(1-phenylsulfonylindol-2-yl)-6-ethyl-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylate (**4b**) Trimethylsilyl iodide (13.5 mmol) was prepared *in situ* as described for **4a**. Compound **3b** (2.81 g, 4.81 mmol) was dissolved in 80 ml of dry CH_2Cl_2 and cooled to 0°C. The freshly prepared TMSI was slowly

syringed into the reaction flask and the solution was allowed to stir for 30 min at 0°C and for 60 min at rt. The progress of the reaction was monitored by TLC. When **3b** was consumed, the reaction mixture was processed as for **4a** to yield 1.32g (61%) of **4b** that was >80% the *exo* stereoisomer. ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 7.73 (m, 1H), 7.57 (d, 1H, J = 7.5Hz), 7.51 - 7.11 (m, 7H), 7.05 (s, 1H), 6.11 (d, 1H, J = 5.4 Hz), 4.08 (s, 1H), 3.58 (s, 3H), 2.92 (dt, 1H, J_1 = 13.4 Hz, J_2 = 3.2 Hz), 2.71 (m, 2H), 2.65 (d, 1H, J = 9.7 Hz), 2.41 (dt, 1H, J_1 = 9.4 Hz, J_2 = 2.4 Hz), 2.10 + 2.04 (m + m', 2H), 1.11 (t, 3H, J = 7.5 Hz). MW calcd. for $C_{25}H_{26}N_2O_4S$ (450.56), found MS (CI) m/z 451 ($M+1^+$).

(±) Methyl 7-*exo*-(1-phenylsulfonylindol-2-yl)-2-chloroacetyl-6-ethyl-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylate (5b) The deprotected amine **4b** (1.02 g, 2.27 mmol) was dissolved in 80 ml of CH_2Cl_2 and converted to **5b** as described for **5a**, except that diisopropylethylamine was used in place of Et_3N. The crude product was purified by flash column chromatography on silica gel (EtOAc: hexane 1:1) to give 0.97 g (81%) of **5b**, mp. 74-76°C. ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 7.64 (m, 1H), 7.51 - 7.29 (m, 4H), 7.29 (t, 2H, J = 7.8 Hz), 7.16 (s, 1H), 7.11 (m, 2H), 6.10 (dd, 1H, J_1 = 6.3 Hz, J_2 = 1.5 Hz), 5.64 (d, 1H, J = 1.5 Hz), 3.84 (d, 2H, J = 1.0 Hz), 3.59 (s, 3H), 3.20 (dd, 1H, J_1 = 8.8 Hz, J_2 = 1.5 Hz), 3.17 - 2.91 (m, 4H), 2.19 - 2.05 (m, 3H), 1.07 (t, 3H, J = 7.3 Hz). MW calcd. for $C_{27}H_{27}ClN_2O_4S$ (527.04), found MS (CI) m/z 527, 529 (3 : 1) ($M+1^+$).

(±) Methyl 2-(chloroacetyl)-6-ethyl-7-*exo*-(indol-2-yl)-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylate (6b) Chloroacetamide **5b** (0.500 g, 0.950 mmol) was desulfonylated as described for **6a**. The crude material was purified by flash column chromatography on silica gel (7% EtOAc in CH_2Cl_2) to yield 0.243 g (66%) of **6b**. ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 9.21 (bs, 1H), 7.53 (d, 1H, J = 6.3 Hz), 7.39 (d, 1H, J = 7.8 Hz), 7.17 (t, 1H, J = 6.4 Hz), 7.05 (t, 1H, J = 7.3 Hz), 6.42 (s, 1H), 6.16 (d, 1H, J = 5.9 Hz), 5.90 (s, 1H), 3.82 (dd, 2H, J_1 = 16.5Hz, J_2 = 10.5 Hz), 3.61 (s, 3H), 3.39 (s, 1H), 3.31 (d, 1H, J = 9 Hz), 3.15 (d, 1H, J = 9 Hz), 3.01 - 2.93 (m, 2H), 2.25 - 2.11 (m, 3H), 1.07 (t, 3H, J = 7.3 Hz). MW calcd. for $C_{21}H_{23}ClN_2O_3$ (386.88), found MS (CI) m/z 387, 389 (3 : 1) ($M+1^+$).

[2,1]-Lactam (7b) Chloroacetamide **6b** (0.071 g, 0.183 mmol) was cyclized using NaH in THF as described for **7a** to give 0.052 g (81%) of **7b**. An analytical sample was purified by flash chromatography (10% EtOAc in CH_2Cl_2), and recrystallized from EtOAc and hexane, mp. 242-244°C (decomp). ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 7.50 (d, 1H, J = 7.8 Hz), 7.36 (d, 1H, J = 8.4 Hz), 7.23 (dt, 1H, J_1 = 8.1 Hz, J_2 = 1.0 Hz), 7.10 (dt, 1H, J_1 = 7.8 Hz, J_2 = 1.0 Hz), 6.36 (dd, 1H, J_1 = 6.6 Hz, J_2 = 1.2 Hz), 5.28 (d, 1H, J = 14.1 Hz), 5.18 (s, 1H), 5.01 (d, 1H, J = 14.1 Hz), 3.66 (dd, 1H, J_1 = 10.5 Hz, J_2 = 2.7 Hz), 3.61 (s, 3H), 3.07 - 2.85 (m, 3H), 2.22 (q, 2H, J = 7.5 Hz), 1.76 (dd, 1H, J_1 = 13.8 Hz, J_2 = 1.0 Hz), 1.09 (t, 3H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) 172.26, 169.95, 142.77, 140.56, 137.60, 130.39, 127.98, 122.70, 120.87, 120.77, 110.01, 103.42,

55.76, 54.63, 53.10, 51.81, 50.27, 35.37, 31.44, 27.32, 11.81. MW calcd. for $C_{21}H_{22}N_2O_3$ (350.42), found MS (CI) m/z 351 ($M+1^+$). Anal. Calcd.: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.95; H, 6.40; N, 7.90.

[2,1]-Analog (8b) Lactam **7b** (0.100 g, 0.28 mmol) was reduced as described for **8a**. The crude amine was obtained as a hard film (89 mg, 93% yield) and subjected to flash chromatography on silica gel (3:1, $CHCl_3$: acetone) to give 52 mg (54% yield) pure **8b**. ^1H NMR ($CDCl_3$, δ ppm 300 MHz) 7.47 (d, 1H, J = 7.8 Hz), 7.27 (d, 1H, J = 7.3 Hz), 7.18 (t, 1H, J = 7.6 Hz), 7.06 (t, 1H, J = 7.3 Hz), 5.94 (~ 2H), 4.58 (ddd, 1H, J_1 = 16.6 Hz, J_2 = 10.0 Hz, J_3 = 3.2 Hz), 4.27 (dt, 1H, J_1 = 15.1 Hz, J_2 = <3Hz), 4.02 (s, 1H), 3.77 (s, 3H), 3.50-3.41 (m, 2H), 3.05-2.78 (m, 4H), 2.32-2.05 (m, 2H), 1.75 (d, 1H, J=13.7 Hz), 1.06 (t, 3H, J=7.3 Hz). ^{13}C NMR ($CDCl_3$) 174.74, 148.08, 137.43, 126.75, 123.88, 121.08, 119.75, 119.25, 108.46, 101.46, 62.89, 56.29, 52.99, 51.61, 49.62, 40.64, 33.04, 29.82, 25.82, 10.34. HRMS (EI) m/z calcd for $C_{21}H_{24}N_2O_2$ (336.1838), found 336.1828 (M^+).

±-20-Deethyl-5-oxocatharanthine **9a** Chloroacetamide **6a** (500 mg, 1.4 mmol) was dissolved in 900 ml of MeOH and 820 mg of $NaHCO_3$ was added. The solution was photolyzed under nitrogen for 6 h using a 450 W mercury-arc Hanovia lamp in a quartz immersion well with a Vycor filter sleeve. The methanol was evaporated, yielding a solid which was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was dried over K_2CO_3 and subjected to flash chromatography (EtOAc: hexane = 1:1.5) to yield 202 mg (45%) of **9a** as an off-white solid. m.p. 295-296°C; lit[8] 292-294°C. ^1H NMR ($CDCl_3$, δ ppm, 300 MHz): 8.06 (bs, 1 H), 7.56 (d, 1 H, J = 7.5 Hz), 7.27 (d, 1 H, J = 7.5 Hz), 7.21 - 7.11 (m, 2 H, J = 7.5 Hz), 6.68 (t, 1 H, J = 7.5 Hz), 6.49 (t, 1 H, J = 7.5 Hz), 5.33 (d, 1 H, J = 6.3 Hz), 4.17 (d, 1 H, J = 15.6 Hz), 3.78 (d, 1 H, J = 15.6 Hz), 3.67 (s, 3 H), 3.59 (dd, 1 H, J_1 = 10.7, J_2 = 3 Hz), 3.00 (d, 1 H, J = 10.7 Hz), 2.95 (m, 1 H), 2.65 (dt, 1 H, J_1 = 13.4 Hz, J_2 = 4 Hz), 1.80 (d, 1 H, J = 13.4 Hz). MW calcd for $C_{19}H_{18}N_2O_3$ (322.2) found MS (CI) m/z 323 ($M+1^+$).

±-20-Deethylcatharanthine **10a** Lactam **9a** (460 mg, 1.43 mmol) was dissolved in 70 ml dry THF. $NaBH_4$ (2.35 g, 62.2 mmol) was added in one portion. The reaction mixture was cooled to 0°C and $BF_3 \cdot OEt_2$ (11.2 ml, 90 mmol) was syringed in dropwise slowly at 0°C and the mixture (yellow suspension) stirred at room temperature for 3 h under nitrogen. The THF was evaporated and methanol (50 ml), H_2O (10 ml) and 10% HCl (5 ml) were added. This acidic solution was stirred at room temperature for 4 h. The methanol was evaporated and the residue mixed with CH_2Cl_2 and 10% NaOH at pH 8-9. The water layer was extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous K_2CO_3 and concentrated to a yellow foam (438 mg, 99.6%). The purity was checked by TLC (pure EtOAc). m.p. 155-160°C; lit[8] 155-160°C. ^1H NMR ($CDCl_3$, δ ppm, 300 MHz): 7.72 (bs, 1 H), 7.48 (d, 1 H, J = 7.5 Hz), 7.25 (d, 1 H, J = 7.5 Hz), 7.15 (t, 1 H, J = 7.5 Hz), 7.10 (t, 1 H, J = 7.5 Hz), 6.60 (t, 1 H, J = 7.5 Hz), 6.39 (t, 1 H, J = 7.5 Hz), 4.38 (d, 1 H, J = 6.2 Hz), 3.75 (s, 3 H), 3.55 (m, 1 H), 3.26 - 3.88 (m, 2 H), 2.91 (m, 1 H), 2.90 (s, 2 H), 2.76 (m, 1 H), 2.69 (d, 1 H, J = 13 Hz), 1.83 (dd, 1

H, J_1 = 13.5 Hz, J_2 = 2 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 174.7, 135.9, 135.1, 134.8, 133.1, 129.0, 121.9, 119.5, 118.2, 110.7, 110.5, 56.8, 55.5, 53.0, 52.6, 48.8, 38.2, 30.7, 21.3. MW calcd for $C_{19}H_{20}N_2O_2$ 308.15, found MS (CI) m/z: 309 ($M+1^+$).

(±)-5-Oxocatharanthine **9b** To a 190 ml photolysis cell was added **5b** (90 mg, 0.170 mmol), 1,5-dimethoxynaphthalene (94 mg, 0.499 mmol), $NaBH_3CN$ (10 mg, 0.159 mmol), and $NaHCO_3$ (100 mg, 1.19 mmol) in 190 ml of methanol. The solution was irridated under nitrogen with light from a 450 W Hanovia lamp for 5 h (Vycor filter)The methanol was removed by rotary evaporation and the residue partitioned between CH_2Cl_2 and water. The organic phase was dried (K_2CO_3) and concentrated. The residue was chromatographed on silica gel (10% EtOAc in CH_2Cl_2) to yield 15 mg (25%) of **9b**. This material was then crystallized from acetone and hexane. This compound matched the expected ^{1}H NMR and MS data.[10] ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz): 7.97 (bs, 1H), 7.56 (d, 1H, J = 7.3 Hz), 7.27 - 7.10 (m, 3H), 6.26 (d, 1H, J = 6.4 Hz), 5.11 (s, 1H), 4.20 (d, 1H, J = 15.6 Hz), 3.78 (d, 1H, J = 15.2 Hz), 3.66 (s, 3H), 3.54 (dd, 1H, J_1 = 10.2 Hz, J_2 = 2.4 Hz), 2.95 (d, 1H, J = 10.3 Hz), 2.90 (m, 1H), 2.71 (m, 1H), 2.28 (q, 2H, J = 6.8 Hz), 1.77 (d, 1H, J = 13.2 Hz), 1.10 (t, 3H, J = 7.3 Hz). MW calcd. for $C_{21}H_{22}N_2O_3$ (350.42), found MS (CI) m/z 351 ($M+1^+$).

Methyl 2-Chloropropenoate[31] To a 100 ml one-neck round-bottom flask charged with methyl 2,3-dichloropropionate[32] (12.0 ml, 71.0 mmol), a solution (in 40 ml water) of $NaHCO_3$ (15.0 g, 141 mmol) and *tetra*-butylammonium bromide (1.26 g, 3.90 mmol) was added. A small amount (about 20 mg) of phenothiazine, along with 30 ml of CH_2Cl_2, was added. This mixture was refluxed for 1.5 h. The mixture was cooled to room temperature and the layers were separated. The organic phase was dried over $MgSO_4$ and carefully concentrated by rotary evaporation. The residue was distilled at 55°C under aspirator pressure into a flask (cooled to 0°C) containing a small amount of hydroquinone to yield 5.68 g (66%) of **10a** a colorless liquid. ^{1}H NMR ($CDCl_3$, δ ppm, 300MHz): 6.53 (d, 1H, J = 1.5 Hz), 6.01 (d, 1H, J = 1.5 Hz), 3.85 (s, 3H).

Methyl 2-benzyloxycarbonyl-7-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate (**11a** and **12a**) Dihydropyridine **2a** (8.9 g, 41.3 mmol), **10a** and hydroquinone (50 mg) were mixed in 1 ml of dry toluene. This mixture was stirred at 80-85°C under argon for 36-48 h. After cooling, the solvents and unreacted dienophile was removed by vacuum pump. The residue was purified by flash column chromatography (silica gel, 25% EtOAc in hexane) and gave 4.46 g (34%) of the *endo*-chloro adduct **12a** and 3.34 g (25%) of the *exo*-chloro adduct **11a**. The *endo*-chloro adduct elutes before the *exo*-chloro adduct. **12a**: ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 7.43 - 7.29 (m, 5H), 6.59 - 6.41 (m, 2H), 5.27 + 5.23 (d + d', 1H, J = 6.2 Hz), 5.21 - 5.01 (m, 2H), 3.70 + 3.52 (s + s', 3H), 3.27 + 3.20 (dd + dd', 1H, J_1 = 9.9 Hz, J_2 = 1.5 Hz), 3.07 - 2.81 (ca, 3H), 1.84 (dd, 1H, J_1 = 14.4 Hz, J_2 = 2.1 Hz). **11a**: mp. 91°C, lit[11] value mp. = 85-86°C. ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 7.45 -7.29 (m, 5H), 6.47 + 6.45 (t + t', 1H, J = 6.7 Hz), 6.40 - 6.27 (m, 1H), 5.30 (d, 1H, J = 6.0 Hz), 5.25 - 5.11 (m, 2H), 3.77 + 3.76 (s + s', 3H), 3.51 (dt, 1H, J_1 = 10.2 Hz, J_2 = 2.4 Hz), 3.06 (dt,

1H, J_1 = 10.5 Hz, J_2 = 2.5 Hz), 2.93 - 2.83 (ca, 1H), 2.73 (dt, 1H, J_1 = 14.4 Hz, J_2 = 3.0 Hz), 1.98 (dt, 1H, J_1 = 14.4 Hz, J_2 = 3.0 Hz). MW calcd. for $C_{17}H_{18}ClNO_4$ (335.78) (both epimers), found MS (CI) m/z 336, 338 (3 : 1) ($M+1^+$).

Methyl 7-*exo*-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylate hydrogen iodide salt (**15a**) Trimethylsilyl iodide (20 mmol) was prepared *in situ* as described for **4a**. *Exo* adduct **11a** (6.12 g, 0.0183 mol) was dissolved in 50 ml of CH_2Cl_2 and cooled in an ice bath. The freshly prepared TMSI solution was added via syringe. The mixture was stirred at 0°C for 45 min. The reaction was quenched by careful addition of methanol (a total of 5 ml) and the solvents were carefully removed by rotary evaporation and then under vacuum. The residue was treated with acetone/ether to induce crystallization. The solvent mixture was decanted and the remaining solids were dried under vacuum to yield 2.8 g (46%) of **15a**. ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 10.09 (bs, 1H), 9.05 (bs, 1H), 6.71 (t, 1H, J = 7.0 Hz), 6.41 (t, 1H, J = 7.0 Hz), 4.79 (d, 1H, J = 6.0 Hz), 3.80 (s, 3H), 3.57 (d, 1H, J = 10.2 Hz), 3.11 - 3.07 (m, 2H), 2.72 (dt, 1H, J_1 = 14.9 Hz, J_2 = 3.2 Hz), 2.19 (dd, 1H, J_1 = 14.1 Hz, J_2 = 1.8 Hz). MW calcd. for $C_9H_{18}ClINO_2$ (329.5) found MS (CI) m/z 202, 204 (3 : 1) ($M+1^+$) for cation.

2-{1-[2-(Indol-2-yl)-1-oxoethyl]}-7-*exo*-chloro-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylic acid methyl ester (**16a**) Indole-2-acetic acid[33] (1.49 g, 8.5 mmol) and **15a** (2.8 g, 8.5 mmol) were dissolved in 50 ml of dry CH_2Cl_2 and stirred at rt for 5 min. DCCI (3.51 g, 17.0 mmol) dissolved in an additional 50 ml of CH_2Cl_2 was added. The reaction mixture was allowed to stir overnight at room temperature. The solution was filtered to remove the urea by-product. The filtrate was washed with dilute HCl (10 ml), $NaHCO_3$ (10 ml), and water (10 ml). The organic phase was dried over $MgSO_4$ and concentrated. The crude material was subjected to flash column chromatography (silica gel, 1:1 EtOAc: hexane) to yield 1.77 g (58 %) of **16a** as a gummy material. ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 9.13 + 9.05 (bs + bs', 1H), 7.53 (t, 1H, J = 6.6 Hz), 7.32 (d, 1H, J = 8.1 Hz), 7.13 (dt, 1H, J_1 = 7.7 Hz, J_2 = 1.1 Hz), 7.06 (t, 1H, J = 7.4 Hz), 6.49 + 6.47 (t + t', 1H, J = 7.5 Hz), 6.35 + 6.29 (s + s', 1H), 6.31 + 6.23 (t + t', 1H, J = 6.3 Hz), 5.78 + 5.04 (d + d', 1H, J = 6.0 Hz), 4.06 (dd, 2H, J_1 = 35.0 Hz, J_2 = 16.0 Hz), 3.66 + 3.57 (dd + dd', 1H, J_1 = 9.3 Hz, J_2 = 2.2 Hz), 3.20 = 3.12 (dt + dt', 1H, J_1 = 9.0 Hz, J_2 = 2.5 Hz), 2.94 (ca, 1H), 2.79 - 2.70 (m, 1H), 1.98 (m, 1H). MW calcd. for $C_{19}H_{19}ClN_2O_3$ (358.81), found MS (CI) m/z 359, 361 (3 : 1) ($M+1^+$).

Deethyllactam (**17a**) A 500 ml photolysis cell was charged with **16a** (0.500 g, 1.39 mmol) and $NaHCO_3$ (0.228 g, 2.71 mmol) dissolved in 350 ml of methanol and 150 ml of water. The reaction cell was continuously purged with nitrogen and irradiated with ultraviolet light from a 400W Hanovia mercury pressure lamp with a Vycor filter for 5 h. The cell was drained and as much of the methanol was removed by rotary evaporation as possible. The remaining aqueous solution was extracted with EtOAc (4 x 70 ml) and the extract dried over $MgSO_4$. The crude material was crystallized with a minimal amount of hot EtOAc to yield

0.105 g (23%) of **17a** mp. >300°C (decomp). ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 9.10 (s, 1H), 7.45 (d, 1H, J = 8.1 Hz), 7.30 (d, 1H, J = 8.1 Hz), 7.13 (t, 1H, J = 7.4 Hz), 7.04 (t, 1H, J = 7.2 Hz), 6.77 (t, 1H, J = 7.0 Hz), 6.38 (t, 1H, J = 7.0 Hz), 5.33 (d, 1H, J = 7.2 Hz), 4.53 (d, 1H, J = 15.6 Hz), 3.61 (~ 1H), 3.57 (s, 3H), 3.51 (d, 1H, J = 15.6 Hz), 3.06 - 2.98 (~ 3H), 1.69 (d, 1H, J = 11.7 Hz). ^{13}C NMR ($CDCl_3$) 174.01, 173.00, 139.69, 135.73, 128.39, 127.59, 126.27, 122.46, 120.42, 119.59, 114.50, 111.50, 53.60, 53.01, 52.66, 50.72, 37.08, 32.86. MW calcd. for $C_{19}H_{18}N_2O_3$ (322.36), found MS (CI) m/z 323 ($M+1^+$). Anal. Calcd.: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.84; H, 5.69; N, 8.60.

Deethyl[3,2]-analog (18a) Lactam **17a** (0.100 g, 0.31 mmol) was suspended in 15 ml dry THF (under argon). $NaBH_4$ (0.51 g, 13.5 mmol) was added in one portion. The reaction vessel was cooled to 0°C in an ice bath. BF_3-OEt_2 (2.4 ml, 19.5 mmol) was added dropwise by syringe. The ice bath was removed and the mixture was stirred at room temperature for 2-3 h. The solvents were removed *in vacuo*. The residue was partitioned between $CHCl_3$ and water. The organic layer was dried (Na_2SO_4) and concentrated. This residue was dissolved in 5 ml of methanol and 100 mg of dry Na_2CO_3 was added. This mixture was refluxed for 1 h under an argon atmosphere. The methanol was removed *in vacuo* and the residue was partitioned between $CHCl_3$ and water. The organic phase was dried (Na_2SO_4) and concentrated to give nearly pure **18a** (89 mg, 93% yield). The material was subjected to flash column chromatography on silica gel (acetone) to give 52 mg (54% yield) of pure **18a**. ^{1}H NMR ($CDCl_3$, δ ppm, 300MHz): 7.82 (bs, 1H), 7.30 (d, 1H, J = 8.1 Hz), 7.26 (d, 1H, J = 8.1 Hz), 6.54 - 6.43 (m, 2H), 4.42 (d, 1H, J = 5.4 Hz), 3.63 (s, 3H), 3.35 - 3.20 (m, 3H), 3.11 - 2.99 (m, 4H), 2.77 (d, 1H, J = 7.8 Hz), 1.68 (dd, 1H, J_1 = 12.8 Hz, J_2 = 2.0 Hz). ^{13}C NMR ($CDCl_3$) 175.59, 135.30, 134.63, 134.27, 133.92, 127.84, 121.85, 120.12, 119.05, 115.61, 110.88, 58.19, 52.91, 52.75, 51.78, 36.92, 31.47, 26.65. HRMS (EI) m/z calcd. for $C_{19}H_{20}N_2O_2$ (308.1525), found 308.1519 (M^+).

Methyl 2-benzyloxycarbonyl-7-*exo*-chloro-6-ethyl-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylate (11b) Dihydropyridine **2b** (7.05 g, 0.0287 mol), methyl 2-chloroacrylate (3.46 g, 0.0287 mol), and a small amount of hydroquinone (25 mg) were dissolved in 2 ml of dry toluene and stirred at 80°C for 24-36 h. The toluene and unreacted acrylate was removed by vacuum pump. The material was purified by flash chromatography on silica gel (1:4 EtOAc:hexane) to yield 3.67g (35%) of the *exo*-chloro adduct (**11b**) (approximately the same amount of the *endo*-chloro adduct **12b** was formed). The *endo*-chloro adduct has a slightly higher R_f and elutes before the *exo*-chloro adduct **11b**: ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 7.40 - 7.30 (m, 5H), 6.05 - 5.98 (m, 1H), 5.18 (d, 1H, J = 1.4Hz), 3.77 +3 .76 (s + s', 3H), 3.46 + 3.43 (dd + dd', 1H, J_1 = 10.2Hz, J_2 =2.1 Hz), 3.03 + 2.99 (q+q', 1H, J = 2.4Hz), 2.86 - 2.78 (m, 1H), 2.77 + 2.72 (q + q', 1H, J = 2.4Hz), 2.11 (dq, 2H, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 1.98 + 1.93 (d + d', 1H, J_1 = 2.1, J_2 = 1.8Hz), 1.00 + 0.96 (t+t', 3H, J = 7.2Hz). MW calcd. for $C_{19}H_{22}ClNO_4$ (363.84), found MS (CI) m/z 364, 366 (3:1) ($M+1^+$).

Methyl 7-*exo*-chloro-6-ethyl-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylate hydrogen iodide salt (**15b**) *Exo*-Chloro adduct **11b** (3.50 g, 9.62 mmol) was dissolved in 20 ml of CH_2Cl_2 and cooled with an ice bath. It was deprotected using TMSI as described for **15a** to yield 1.48 g (47.6%) of **15b**. ^{1}H NMR (d_6-DMSO, δ ppm, 300MHz) 9.45 (bs, 1H), 8.86 (bs, 1H), 6.27 (d, 1H, J = 6.0 Hz), 4.58 (s, 1H), 3.72 (s, 3H), 3.20 (m, 1H), 3.01 (m, 1H), 2.69 (m, 1H), 2.12 (q, 2H, J = 7.2 Hz), 0.93 (t, 3H, J = 7.2 Hz). MW calcd for $C_{11}H_{17}ClINO_2$(357.62), found MS (CI) m/z 230 (cation).

Methyl 2-{1-(indol-2-yl)-1-oxoethyl)}-7-*exo*-chloro-6-ethyl-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylate (**16b**) The hydrogen iodide salt **15b** (1.26 g, 4.05 mmol) was converted to **16b** as described for **16a** to give 2.99 g crude **16b**. This material was purified by flash chromatography on silica gel (EtOAc: hexane = 1:1) to yield 1.20 g (76.7%) of pure **16a** as a gummy material. ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 9.12 + 9.04 (bs + bs', 1H), 7.53 + 7.52 (d + d', 1H, J = 7.5Hz), 7.32 (d, 1H, J = 8.1Hz), 7.13 (t, 1H, J = 7.5Hz), 7.06 (t, 1H, J = 7.8Hz), 6.37 + 6.29 (s + s', 1H), 6.12 + 6.03 (dd + dd', 1H, J_1 = 6.6Hz, J_2 = 1.5,), 5.64 + 4.86 (d + d', 1H, J =1.5Hz), 4.08 (dd, 1H, J = 15.3, 35.7Hz), 3.81 + 3.77 (s + s', 3H), 3.62 + 3.59 (d + d', 1H, J = 2.1Hz), 3.54 + 3.50 (d + d', 1H, J = 2.1Hz), 3.10 + 3.06 (dt + dt', 1H, J_1 = 10.8Hz, J_2 = 2.7 Hz,), 2.89 (~ 1H), 2.82 - 2.72 (m, 1H), 2.13 (q, 2H, J = 6.3Hz), 2.08 - 1.90 (m, 2H), 0.97 + 0.87 (t + t', 3H, J = 7.5Hz). MW calcd. for $C_{21}H_{23}ClN_2O_3$ (386.8), found MS (CI) m/z 387, 389 (3 : 1) ($M+1^+$).

[3,2]-Lactam **17b** A 500 ml photolysis cell was charged with **16b** (0.500 g, 1.29 mmol) and $NaHCO_3$ (0.228 g, 2.71 mmol) that had been dissolved in 350 ml of methanol and 150 ml of water. The reaction cell was purged with nitrogen while irradiated with ultraviolet light from a Hanovia mercury pressure lamp with a Vycor filter for 5 h. The product was isolated as for **17a** to yield 0.105 g (23%) of **17b**, mp. 297°C (decomp). ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 8.61 (bs, 1H), 7.41 (d, 1H), 7.30 (d, 1H, J = 8.1 Hz), 7.14 (dt, 1H, J_1 = 7.5Hz, J_2 = 1.1 Hz), 7.04 (dt, 1H, J_1 = 7.5Hz,J_2 = 1.1 Hz), 6.31 (dd, 1H, J_1 = 7.2Hz, J_2 = 1.2 Hz), 5.08 (s, 1H), 4.58 (d, 1H, J = 15.6Hz), 3.55 (s, 3H), 3.53 (~ 1H), 3.49 (d, 1H, J = 15.6Hz), 3.07 - 2.98 (m, 1H), 2.95 (dd, 2H, J_1 = 11.4 Hz, J_2 = 2.1 Hz), 2.20 (dq, 2H, J_1 = 7.2 Hz,J_2 = 1.8 Hz), 1.61 (d, 1H, J = 12.9Hz), 1.10 (t, 3H, J = 7.5Hz). ^{13}C NMR ($CDCl_3$) 173.82, 173.05, 142.83, 135.69, 129.81, 127.55, 126.21, 122.43, 120.39, 119.44, 114.96, 111.46, 58.08, 52.73, 52.49, 51.55, 37.15, 33.41, 32.61, 27.27, 11.81. MW calcd. for $C_{21}H_{22}N_2O_3$ (350.42), found MS (CI) m/z 351 ($M+1^+$). Anal. Calcd.: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.02; H, 6.36; N, 7.97.

[3,2]-Analog **18b** Lactam **17b** (0.100 g, 0.28 mmol) was suspended in 15 ml of dry THF. Reduction was carried out as for **18a** to give **18b** (89 mg, 93% yield). Pure material was obtained by flash chromatography on silica gel (1:1, $CHCl_3$ acetone) to give 52 mg (54% yield) of **18b**. ^{1}H NMR ($CDCl_3$, δ ppm 300 MHz) 7.82 (s, 1H), 7.26 (d, 1H, J = 7.3 Hz), 7.24 (d, 1H, J = 6.3 Hz), 7.11 (t, 1H, J = 7.6 Hz), 7.00 (t, 1H, J = 7.1 Hz), 5.96 (d, 1H, J = 6.4 Hz), 4.14 (s, 1H), 3.66 (m, 1H), 3.61 (s, 3H), 3.35 - 3.20 (m, 2H), 3.05 (dt, 2H, J_1

= 13.2 Hz, J_2 = 2.9 Hz), 2.91 (m, 1H), 2.79 (d, 2H, J = 8.3 Hz), 2.29 + 2.02 (m + m', 2H), 1.63 (d, 1H, J = 13.0 Hz), 1.07 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) 174.56, 147.87, 134.55, 133.20, 127.12, 123.25, 120.97, 119.20, 118.16, 115.44, 109.98, 62.57, 52.01, 51.67, 51.58, 51.07, 37.07, 30.67, 25.94, 10.23. HRMS (EI) m/z calcd. for $C_{21}H_{24}N_2O_2$ (336.1838), found 336.1844 (M^+).

Methyl 2-bromopropenoate (10b) In a 500 ml flask, Na_2CO_3 (34.26 g, 0.324 mol) and tetrabutylammonium bromide (2.38 g, 7.37 mmol) were dissolved in 200 ml of water. A small amount of phenothiazine and methyl 2,3-dibromopropionate[34] (36.26 g, 0.147 mol) were dissolved in 100 ml of CH_2Cl_2 and added to the flask. This mixture was stirred at reflux for 30 min, cooled and the layers separated. The organic layer was dried over $MgSO_4$ and carefully concentrated by rotary evaporation. The pure ester was obtained by low pressure distillation (hydroquinone was added to the collection flask as a stabilizer). **10b** was obtained (18.2 g, 75%) as a clear liquid. ^{1}H NMR ($CDCl_3$, δ ppm, 300MHz): 6.96 (d, 1H, J = 1.5 Hz), 6.27 (d, 1H, J = 1.5 Hz), 3.84 (s, 3H).

Methyl 2-benzyloxycarbonyl-7-bromo-2-azabicyclo[2.2.2]oct-5-ene-7-carboxylate (13a,14a) Methyl 2-bromopropenoate (4.0 ml, 0.039 mol) and **2a** (9.49 g, 0.044 mol) were mixed with a small amount of hydroquinone and heated at 50°C overnight. Reaction progress was slow as determined by TLC (EtOAc: hexane = 4:1). The temperature was raised to 75°C and the reaction was allowed to stir for an additional 24 h. The reaction vessel was cooled and unreacted materials were removed by vacuum pump. After flash column chromatography (silica gel, 1:4 EtOAc:hexane) 2.26 g (15.2%) of *exo*-bromo adduct **13a** was obtained as an oil. **13a**: ^{1}H NMR ($CDCl_3$, δ ppm, 300MHz): 7.42 - 7.28 (m, 5H), 6.45 (dd (both rotamers), 1H, J_1 = 12.3 Hz, J_2 = 5.4 Hz), 6.39 - 6.30 (m (both rotamers), 1H), 5.37 (d, 1H, J = 5.7 Hz) + 5.25 (d', 1H, J = 6.0 Hz), 5.22 - 5.15 (m, 2H), 3.76 (s, 3H) + 3.75 (s', 3H), 3.54 - 3.48 (m, 1H), 3.08 (t, 1H, J = 2.6 Hz) + 3.04 (t', 1H, J = 2.7 Hz), 2.90 - 2.81 (ca, 1H), 2.80 (d, 1H, J = 2.7 Hz) + 2.75 (δ', 1H, J = 2.4 Hz), 2.20 (t, 1H, J = 1.8 Hz) + 2.15 (t', 1H, J = 1.8Hz). *Endo*-Bromo adduct **14a**: ^{1}H NMR ($CDCl_3$, d ppm, 300MHz): 7.44 - 7.28 (~ 5H), 6.55 - 6.45 (m, 2H), 5.38 (m, 1H) + 5.31 (d', 1H, J = 6.0 Hz), 5.24 (d, 1H, J = 12.0 Hz) + 5.07 (d', 1H, J = 12.0 Hz), 3.68 (s, 3H) + 3.53 (s', 3H), 3.24 (dd, 1H, J_1 = 10.5 Hz, J_2 = 2.1 Hz), 3.10 - 2.93 (ca, 2H), 2.90 - 2.79 (ca, 1H), 2.03 (d, 1H, J = 15 Hz). MW calcd. for $C_{17}H_{18}BrNO_4$ (380.23) (both isomers), found MS (CI) m/z 380, 382 (1 :1) ($M+1^+$).

Methyl 7-*exo*-bromo-2-azabicyclo[2.2.2]oct-5-ene-7-*endo*-carboxylate hydrogen bromide salt (15c) 30% wt HBr in acetic acid (10 ml) was added dropwise by syringe to **13a** (2.26 g, 5.94 mmol). The mixture was stirred at rt (under argon) until all the starting material was consumed, as determined by TLC. The AcOH/HBr and some benzyl bromide were removed under vacuum. The residue was treated with acetone to induce crystallization. The crystals were collected to yield 1.09 g (56%) of **15c**. ^{1}H NMR (d_6-DMSO, δ ppm, 300MHz) 6.71 (t, 1H, J = 7.5 Hz), 6.29 (t, 1H, J = 7.5 Hz), 4.76 (d, 1H, J = 6.0 Hz), 3.71 (s, 3H), 3.27 (d, 1H, J = 12.3 Hz), 3.01 (ca, 1H), 2.71 (dt, 1H, J_1 = 11.1 Hz, J_2 = 2.4 Hz), 2.56 (dt, 1H, J_1 = 15.0

Hz, J_2 = 3.1 Hz), 2.25 (dd, 1H, J_1 = 15.0 Hz, J_2 = 2.1 Hz).

Methyl 2-{1-[2-(indol-2-yl)-1-oxoethyl]}-7-*exo*-bromo-2-azabicyclo[2.2.2] oct-5-ene-7-*endo*-carboxylate (**16c**) **Indole-2-acetic acid**[33] **(0.270 g, 1.54 mmol) and** DCC (0.320 g, 1.55 mmol) were suspended in **10 ml of dry** CH_2Cl_2 **and stirred at rt for 5 min. A mixture of** Hunig's Base (0.30 ml, 1.72 mmol) and bromide salt **15c** (0.500 g, 1.53 mmol) in 5 ml of CH_2Cl_2 was added to the reaction vessel and the mixture was allowed to stir overnight at rt (under argon). The mixture was then filtered and the filtrate was washed with 10 ml of 3% HCl, 3% $NaHCO_3$, and brine. The organic phase was dried (Na_2SO_4) and concentrated. Flash column chromatography (silica gel, 50% EtOAc in hexane) afforded 0.220 g (35%) of **16c** as a brownish foam. ^{1}H NMR ($CDCl_3$, δ ppm, 300MHz): 9.13 + 9.07 (bs + bs', 1H), 7.53 (dd, 1H, J_1 = 6.6 Hz, J_2 = 6.3 Hz), 7.32 (d, 1H, J = 8.1 Hz), 7.14 (dt, 1H, J_1 = 7.5 Hz, J_2 = 1.2 Hz), 7.06 (dt, 1H, J_1 = 7.2 Hz, J_2 = 0.9 Hz), 6.48 (q, 1H, J = 15.0 Hz), 6.35 + 6.30 (d + d', 1H, J = 1.2 Hz), 6.33 + 6.24 (dt + dt', 1H, J_1 = 6.0 Hz, J_2 = 1.5 Hz), 5.85 + 5.12 (d + d', 1H, 6.2Hz), 4.17 - 4.01 (dd, 1H, J_1 = 28.5 Hz, J_2 = 16.2 Hz) + 3.86 (s', 1H), 3.83 + 3.77 (s + s', 3H), 3.67 + 3.56 (dd + dd', 1H, J_1 = 9.3 Hz, J_2 = 2.4 Hz), 2.92 (ca, 1H), 2.82 + 2.78 (q + q', 1H, J = 3.4 Hz), 2.21 + 2.16 (dd + dd', 1H, J_1 = 9.9 Hz, J_2 = 2.1Hz). MW calcd. for $C_{19}H_{19}BrN_2O_3$ (403.27), found MS (CI) m/z 403, 405 (1 : 1) ($M+1^+$).

N-Methylcatharanthine (**10c**). **Catharanthine** (100 mg, 0.3 mmol) was added to a suspension of NaH (7 mg, 0.3 mmol, 80%/wt suspension in mineral oil) in 3 ml of THF at 0°C. The solution was heated for 5 min at reflux to complete evolution of H_2 and then recooled to 0°C. Methyl iodide (19 µl, 0.3 mmol) was added. The solution was allowed to stir at 0°C for 30 min and at rt for 30 min. The solvent was removed by rotary evaporation and the residue was partitioned between CH_2Cl_2 and water. The organic layer was dried (Na_2SO_4) and concentrated. The product was separated from unreacted **10b** by radial chromatography (1:1 EtOAc:hexane) to give 21 mg (20 %) of **10c** as a film. ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz): 7.54 (d, 1H, J = 7.8 Hz), 7.26 - 7.10 (m, 3H), 6.05 (d, 1H, J = 5.9 Hz), 4.55 (s, 1H), 3.71 (m, 1H), 3.59 (s, 3H), 3.50 (s, 3H), 3.30 (ddd, 1H, J_1 = 18 Hz, J_2 = 13 Hz, J_3 = 5 Hz), 3.13 - 3.05 (m, 2H), 3.01 (dt, 1H, J_1 = 13.9 Hz, J_2 = 2.0 Hz), 2.95 - 2.85 (m, 2H), 2.75 (m, 1H), 2.50 (d, 1H, J = 8.3 Hz), 2.35 + 1.97 (dq + dq, 2H, J_1 = 16.6 Hz, J_2 = 7.3 Hz), 1.72 (d, 1H, J = 12.1 Hz), 1.09 (t, 3H, J = 7.1 Hz).

Amine oxide, **22b**. **18b** (56 mg, 0.166 mmol) was dissolved in 5 ml of dry CH_2Cl_2 and cooled to 0°C. *m*-Chloroperoxybenzoic acid (MCPBA) (34 mg, 0.166 mmol) was added in one portion. The mixture was allowed to stir at 0°C for 45 min. At this point TLC (2:1 $CHCl_3$:acetone) showed that all starting material had been consumed. The $CH_2Cl_2$was removed by rotary evaporation and the residue dried in vacuum to yield 85 mg (94%) of a greenish film. ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz): 9.48 (s, 1H), 8.06 (s, 1H), 7.96 (d, 1H, J = 8.0 Hz), 7.56 (d, 1H, J = 8.0 Hz), 7.40 (t, 1H, J = 7.8 Hz), 7.30 (d, 1H, J = 8.1 Hz), 7.23 (d, 1H, J = 8.1 Hz), 7.10

(t, 1H, J = 7.5 Hz), 7.04 (t, 1H, J = 7.5 Hz), 6.27 (t, 1H, J = 5.9 Hz), 5.12 (dd, 1H, J_1 = 14.0 Hz, J_2 = 6.9 Hz), 4.17 (dd, 1H, J_1 = 17.7 Hz, J_2 = 10.2 Hz), 3.96 (dd, 1H, J_1 = 12.4 Hz, J_2 = 10.2 Hz), 3.92 - 3.76 (m, 3H), 3.45 (s, 3H), 3.30 - 3.11 (m, 3H), 2.50 + 2.26 (dq + dq, 2H, J_1 = 7.5 Hz, J_2 = 2.1 Hz), 1.56 (d, 1H, J = 13.4 Hz), 1.11 (t, 3H, J = 7.5 Hz). MW calcd. for $C_{21}H_{24}N_2O_3$ (352.41), found MS (CI) m/z 353 ($M+1^+$).

Amine oxide 22a. **18a** (60 mg, 0.195 mmol) was dissolved in 5 ml of dry CH_2Cl_2 and cooled to 0°C. MCPBA (39 mg, 0.195 mmol) was added in one portion. The mixture was allowed to stir at 0°C for 45 min. The CH_2Cl_2 was removed by rotary evaporation and the product dried in vacuum to yield 96 mg (96%) of a greenish film. ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz): 9.77 (s, 1H), 9.40 - 8.60 (bs, 1H), 8.04 (s, 1H), 7.93 (d, 1H, J = 7.5 Hz), 7.47 (d, 1H, J = 7.5 Hz), 7.33 (t, 1H, J = 8.1 Hz), 7.30 - 7.21 (m, 2H), 7.09 (t, 1H, J = 7.5 Hz), 7.03 (t, 1H, J = 7.5 Hz), 6.66 (t, 1H, J = 7.3 Hz), 6.43 (t, 1H, J = 6.7 Hz), 5.38 (d, 1H, J = 5.4 Hz), 4.92 (m, 1H), 3.96 - 3.71 (m, 4H), 3.51 (s, 3H), 3.26 - 3.05 (m, 3H), 1.53 (d, 1H, 14.0 Hz). MW calcd. for $C_{19}H_{20}N_2O_3$ (324.38), found MS (CI) m/z 325 ($M+1^+$).

Amine oxide 19b. **8b** (18 mg, 0.053 mmol) was dissolved in 2 ml of dry CH_2Cl_2 and cooled to 0°C. MCPBA (11 mg, 0.053 mmol) was added in one portion. The mixture was allowed to stir at 0°C for 25 min. The CH_2Cl_2 was removed by rotary evaporation and the product dried in vacuum to yield 29 mg (100%) of a greenish film.. ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz): 8.05 (s, 1H), 7.93 (d, 1H, J = 8.0 Hz), 7.52 (d, 1H, J = 8.0 Hz), 7.48 (m, 1H), 7.35 (t, 1H, J = 8.1 Hz), 7.28 - 7.10 (m, 3H), 6.21 (d, 1H, J = 5.9 Hz), 6.11 (s, 1H), 4.95 - 4.73 (m, 2H), 4.50- 4.33 (m, 1H), 4.18 (d, 1H, J = 12.4 Hz), 3.84 - 3.80 (ca, 4H), 3.18 - 3.02 (m, 2H), 2.50 + 2.28 (dq + dq, 2H, J_1 = 7.5 Hz, J_2 = 2.1 Hz), 1.71 (d, 1H, J = 14.0 Hz), 1.13 (t, 1H, J = 7.5 Hz). MW calcd. for $C_{21}H_{24}N_2O_3$ (352.41), found MS (CI) m/z 353 ($M+1^+$).

Amine oxide 19a. **8a** (33 mg, 0.107 mmol) was dissolved in 5 ml of dry CH_2Cl_2. and cooled to 0°C. MCPBA (22 mg, 0.107 mmol) was added in one portion. The mixture was allowed to stir at 0°C for 30 min. The CH_2Cl_2 was removed by rotary evaporation and the product dried in vacuum to yield 55 mg (100%) of a greenish film. ^{1}H NMR ($CDCl_3$, δ ppm, 300 MHz): 8.05 (s, 1H), 7.94 (d, 1H, J = 7.0 Hz), 7.55 - 7.47 (m, 2H), 7.35 (t, 1H, J = 8.0 Hz), 7.28 - 7.09 (m, 3H), 6.70 - 6.35 (m, 2H), 6.13 (s, 1H), 5.05 (ca, 1H), 4.89 - 4.82 (m, 2H), 4.50 - 4.39 (m, 2H), 4.22 (d, 1H, J = 12.4 Hz), 3.90 (d, 1H, J = 12.4 Hz), 3.84 (s, 3H), 3.16 (m, 1H), 3.02 (d, 1H, J = 14.5 Hz), 1.77 (d, 1H, J = 14.0 Hz). MW calcd. for $C_{19}H_{20}N_2O_3$ (324.38), found MS (CI) m/z 325 ($M+1^+$).

General Procedure for Ferric Chloride Reactions. In a 50 ml round-bottom three-neck flask 10 ml of 0.10 M glycine solution (7.5 g glycine and 5.85 g sodium chloride in 1000 ml water) was purged with argon for 10 min at room temperature. $FeCl_3 \cdot 6H_2O$ (6 - 30 eq) was added to the flask as a solid.[35] Approximately 15 mg of the appropriate amine was dissolved in 1 ml of methanol and transferred to the flask by pipet. When vindoline was used, 1.0 - 1.2 equivalents was added. The mixture was allowed to stir at rt for 3 h under a constant purge of

argon. Then 1 - 2 eq. of $NaBH_4$ was added in 1-2 ml of concentrated NH_4OH solution and the mixture was allowed to stir for 5 min (NOTE: in some reactions the $NaBH_4$ was deleted to provide a non-reductive workup). The pH was tested with pH paper to be certain that the solution was slightly basic (around pH 8-9). This basic solution was extracted with CH_2Cl_2 (4 x 15 ml), dried (Na_2SO_4) and concentrated under reduced pressure. At this point the ^1H NMR was examined to determine the crude product composition. The products and any unreacted starting material were separated by column chromatography. The isolation procedures, yield and spectroscopic information are listed for individual compounds.

General Procedure for Potier Reactions. Approximately 15 mg of amine-N-oxide as its MCBA salt was dissolved in 1 ml of dry CH_2Cl_2 and transferred by syringe to a 5 ml side-neck flask (under argon) cooled to 0°C. If vindoline was included, 1.0-1.2 eq was dissolved in 0.5 ml of CH_2Cl_2 and added by syringe. The flask was then cooled to -60°C and TFAA (3-5 eq, distilled from P_2O_5 immediately before use) was rapidly added by syringe. The solution was allowed to stir under argon for 3 h at -55°C. The reaction could then be worked up two ways: a) reductive or b) nonreductive. a) Reductive Workup: The CH_2Cl_2 solution was quickly transferred to a cold (-40°C) solution of ethanol and excess $NaBH_4$ or $NaBD_4$ and allowed to stir and warm to room temperature over 5 min. The excess BH_4^- was then quenched with 1-2 ml of acetone. The solvents were removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 and aqueous Na_2CO_3. The organic layer was dried (Na_2SO_4) and concentrated. b) Nonreductive Workup: The reaction was quenched with 0.5 ml of methanol and the solvents were removed by rotary evaporation and dried under vacuum. This residue was then partitioned between CH_2Cl_2 and aqueous Na_2CO_3. The organic layer was dried (Na_2SO_4) and concentrated. The ^1H NMR was examined to determine the crude product composition. The products were separated by column and radial chromatography using 1:5 methanol:EtOAc.

20-Deethylanhydrovinblastine dimers **25a** and **26a**. Glycine solution (10 ml) was purged with argon for 10 min at rt. $FeCl_3 \cdot 6H_2O$ (130 mg, 0.480 mmol) was added to the flask as a solid. Amine **10a** (31 mg, 0.100 mmol) was dissolved in 1 ml of methanol and transferred to the round-bottom flask by pipet. Vindoline (23 mg, 0.50 mmol) was then added as a solid. The mixture was allowed to stir at room temperature for 3 h under argon. $NaBH_4$ (1-2 eq.) was added in 1-2 ml of concentrated ammonium hydroxide solution and the mixture was allowed to stir for 5 min. The pH was checked with pH paper and was 8-9. The basic solution was extracted with CH_2Cl_2 (4 x 15 ml), dried (Na_2SO_4) and concentrated under reduced pressure to give 48 mg (89%) of crude material. At this point the ^1H NMR was examined to determine the amount of coupling. The two "dimers" were present in a 1:1 ratio. All of the vindoline had been consumed and some **10a** was still present. The "dimers" were separated by radial chromatography (silica gel, 1:6 MeOH:EtOAc) **25a**: 12 mg, 25% yield; **26a**:14 mg, 30% yield) and the unreacted **10a** was recovered by preparative layer chromatography (silica gel, 1:6 MeOH:EtOAc). The recovered **10a** (2 mg) was treated with $Eu(hfc)_3$ (4.2 mg, 0.4 equivalents). The ^1H NMR

in $CDCl_3$ showed a 1:1.1 ratio of the indole N-H signals. Dimer **25a** (key assignments): ^{1}H NMR ($CDCl_3$, δ ppm, 300MHz): 8.03 (bs, 1H), 7.52 (d, 1H, J = 7.8 Hz), 7.20 - 7.10 (m, 3H), 6.61 (s, 1H), 6.12 (s, 1H), 5.86 (dd, 1H, J_1 = 10.4 Hz, J_2 = 3.8 Hz), 5.74 (bs, 2H), 5.46 (s, 1H), 5.29 (d, 1H, J = 10.3 Hz), 3.82 (s, 3H), 3.80 (s, 3H), 3.62 (s, 3H), 2.72 (s, 3H), 2.11 (s, 3H), 0.79 (t, 3H, J = 7.3 Hz). Dimer **26a** (key assignments): ^{1}H NMR ($CDCl_3$, δ ppm, 300MHz): 8.08 (s, 1H),7.52 (d, 1H, J = 7.3 Hz), 7.28 - 7.10 (m, 3H), 6.74 (s, 1H), 6.16 (s, 1H), 5.78 (m, 3H), 5.46 (s, 1H), 5.24 (d, 1H, J = 10.0 Hz), 3.81 (s, 3H), 3.80 (s, 3H), 3.56 (s, 3H), 2.73 (s, 3H), 2.07 (s, 3H), 0.37 (t, 3H, J = 7.3 Hz).

Methyl 7*H*-2-(*E*-3-hydroxymethyl-1-butenyl)-1,2,5,6-tetrahydroindolizidino[7,8-b]indole-11c-carboxylate **24b**. The general ferric chloride (25 eq) reductive procedure was used on 15 mg of **18b**. After CH_2Cl_2 extraction from the basified aqueous solution from reductive workup, the crude material was chromatographed on a basic alumina column (CH_2Cl_2 → 30% EtOAc in CH_2Cl_2) to yield 4 mg of recovered **18b** and 4 mg (25%) of **24b**. MW calcd. for $C_{21}H_{26}N_2O_3$ (354.45), found MS (CI) m/z 355 ($M+1^+$).

Methyl 7*H*-2-(*E*-3-formyl-1-butenyl)-1,2,5,6-tetrahydroindolizidino[7,8-b]indole 11c-carboxylate (*E*-**23b**). $FeCl_3 \cdot 6H_2O$ (325 mg, 1.20 mmol) and **18b** (14 mg, 0.0417 mmol) were allowed to react in glycine solution (10 ml) for 3 h under argon. The solution was made basic and processed in the standard way. The crude material was chromatographed on a silica gel column (1:4 MeOH:EtOAc) to give 3 mg of **18b** and 4 mg of *E*-**23b** (27% yield) as a film. MW calcd. for $C_{21}H_{24}N_2O_3$ (354.45), found MS (CI) m/z 355 ($M+1^+$).

Methyl 7*H*-2-(*Z*-3-formyl-1-butenyl-1,2,5,6-tetrahydroindolizidino[7,8-b]indole-11c-carboxylate (*Z*-**23b**). Amine oxide **22b** (18 mg, 0.0354 mmol) was dissolved in 1 ml of dry CH_2Cl_2 and transferred by syringe to a 5 ml side-neck flask (under argon) cooled to 0°C. Et_3N (6 µl, 0.043 mmol) was added by syringe. The flask was then cooled to -60°C and TFAA (3 - 5 eq), was rapidly added by syringe. The solution was allowed to stir under argon for 3 h at -55°C. The reaction was quenched with 1 ml of methanol and the mixture was allowed to stir until the flask reached rt. The crude product (15 mg) was obtained by the usual workup and chromatographed on a silica gel column (1:5 MeOH:EtOAc) to give 1.6 mg (14% yield) of *Z*-**23b** as film. MW calcd. for $C_{21}H_{24}N_2O_3$ (352.44), found MS (CI) m/z 353 ($M+1^+$).

Methyl 7*H*-2-(*E*-3-oxo-1-propenyl)-1,2,5,6-tetrahydroindolizidino[7,8-b]indole-11c-carboxylate (*E*-**23a**). Ferric chloride hexahydrate (512 mg, 1.89 mmol) and **18a** (24 mg, 0.0779 mmol) in 10 ml of glycine solution were allowed to stir at room temperature for 3 h under argon. The solution was made basic (around pH 8-9) and subjected to the standard workup. The crude material was chromatographed on a silica gel column (1:4 MeOH:EtOAc) to give aldehyde *E*-**23a** as a film (5 mg, 26% yield). MW calcd. for $C_{19}H_{20}N_2O_3$ (324.45), found MS (CI) m/z 325 ($M+1^+$).

Dimers (**20a, 21a**). Amine oxide **19a** (15 mg, 0.0312 mmol) was dissolved in 1 ml of dry CH_2Cl_2 and transferred by syringe to a 5 ml side-neck flask (under argon) cooled to 0°C. Vindoline (19 mg, 0.0415 mmol) was dissolved in 0.5 ml of CH_2Cl_2 and added to the flask. The mixture was then cooled to -60°C and TFAA (25 µl,

5.7 eq) was added. The solution was allowed to stir under argon for 3 h at -55°C. The reaction solution was quickly transferred to a cold (-40°C) solution of ethanol and excess $NaBH_4$ and allowed to stir and warm to rt over 5 min. The excess borohydride was then quenched with 1 - 2 ml of acetone. The solvents were removed by rotary evaporation. The residue was partitioned between CH_2Cl_2 and aqueous Na_2CO_3. The CH_2Cl_2 layer was dried (Na_2SO_4) and concentrated to give 22 mg of crude material. The NMR of the crude material indicated approximately 10% of each "coupled" material based on comparison with the vindoline signals. This reaction was repeated twice with similar results. The combined materials were chromatographed by radial chromatography (1:5 MeOH:EtOAc) to give vindoline (24 mg) and the two "dimers" (3 mg, 4.3 %). Dimer **20a** (key assignments): ^{1}H NMR (d_6-acetone, δ ppm, 300MHz): 7.28 (d, 1H, J = 8.3 Hz), 6.99 (dt, 1H, J_1 = 7.6 Hz, J_2 = 1.5 Hz), 6.78 (d, 1H, J = 7.8 Hz), 6.71 (t, 1H, J = 8.3 Hz), 6.56 (s, 1H), 6.20 (s, 1H), 6.11 (m, 2H), 5.71 (dd, 1H, J_1 = 10.3 Hz, J_2 = 3.9 Hz), 5.43 (s, 1H), 5.29 (d, 1H, J = 10.6 Hz), 4.41 (ddd, 2H, J_1 = 15.1 Hz, J_2 = 10.3 Hz, J_3 = 2.1 Hz), 4.36 (ddd, 2H, J_1 = 15.1 Hz, J_2 = 4.9 Hz, J_3 = 2.0 Hz), 4.13 (d, 1H, J = 4.8 Hz), 3.60 (s, 3H), 3.56 (s, 3H), 3.51 (a, 1), 3.44 (m), 3.33 (dd, 1H J = 15.5, J_2 = 5, 3.1-3.3 (m), 3.01 (s, 3H), 2.60 (s, 3H), 2.65 (J = 7.8) 2.0-2.2 (m), 1.86 (s, 3H), 1.80 (d, J = 14.5 Hz), 1.58 (dg, J = 7.5, 1), 0.69 (t, 3H, J = 7.3 Hz). MW calcd. for $C_{44}H_{51}N_4O_8$ (763.87), found MS (EI) m/z 763 (M^+); Dimer **21a** (key assignments): ^{1}H NMR (d_6-acetone, 8 ppm , 300 Mhz): 7.30 (d, J = 8 Hz), 7.00 (t, J = 7 Hz), 6.94 (d, J = 7 Hz); 6.78, 6.76 (t and s); 6.15 (s); 5.90 dd (J = 10, 4 Hz); 5.38 (d, J = 11 Hz) 5.31 (s); 4.4-4.6 (m), 4.09 (m); 3.60 s; 3.56 s; 3.2-3.4 (m) 2.97 (s) 2.6-2.8 (m); 2.62 (s) 2.20 (m): 1.53, 1.65 (AB quartets) 0.69 (t, J = 7 Hz). MW calcd for $C_{44}H_{51}N_4O_8$ (763.87), found MS (EI m/z 763 M^+).

Dimer (20b). Amine oxide **19b** (15 mg, 0.0295 mmol) was dissolved in 1 ml of dry CH_2Cl_2 and transferred by syringe to a 5 ml side-neck flask (under argon) cooled to 0°C. Vindoline (15 mg, 0.0330 mmol) was dissolved in 0.5 ml of CH_2Cl_2 and added by syringe. The flask was then cooled to -60°C and TFAA (19 μl, 4 eq.) was rapidly added. The solution was allowed to stir under argon for 3 h at -55°C. The reaction solution was treated as described for **20a/21a** to give 21 mg of crude material. This reaction was repeated once more with similar results. The combined materials were purified by radial chromatography (silica, 1:5 MeOH:EtOAc) to give unreacted vindoline (17 mg) and **20b** (1 mg, 2.1 %). Key assignments, ^{1}H NMR (d_6-acetone, δ ppm, 300MHz): 7.30 (d, 1H, J = 7.8 Hz), 7.00 (t, 1H, J = 7.8 Hz), 6.78 (t, 1H, J = 7.8 Hz), 6.71 (d, 1H, J = 7.8 Hz), 6.58 (s, 1H), 6.21 (s, 1H), 5.72 (m, 3H), 5.42 (s, 1H), 5.30 (dd, 1H, J_1 = 10.2 Hz, J_2 = 1.0 Hz), 4.41 (m, 2H), 3.61 (s, 3H), 3.56 (s, 3H), 3.03 (s, 3H), 2.60 (s, 3H), 1.87 (s, 3H), 0.85 (t, 3H, J = 7.3 Hz), 0.69 (t, 3H, J = 7.3 Hz). MW calcd. for $C_{46}H_{55}N_4O_8$ (791.94), found MS (EI) m/z 791 (M^+).

Electrochemistry. The voltammetric measurements were performed in a 15 ml conical cell with a glassy carbon electrode (GCE; A = 0.05 cm^2), with platinum as a counter and saturated calomel electrode (SCE) as a reference. Before each measurement GCE was sonicated for 1 min in acetone and polished on a filter paper. All electrochemical measurements were carried out using PAR M-175 electrochemical analysis system and the

voltammograms were recorded on Kipp & Zonen X-Y recorder. The cyclic voltammograms were recorded in the range of 0.015 to 1 V/s. The value of transfer coefficient was obtained from the peak widths for each voltammogram using the following equation.[36]

$$E_p - E_{p/2} = 1.857\ (RT/\alpha nF)$$

For each voltammogram the peak current and transfer coefficient were measured and assuming the value of the diffusion constant for DECATH (D = 1.4x10-5 cm^2/s) the apparent number of electrons n was calculated at different sweep rates using the following equation.[37]

$$i_p = (2.99 \times 10^5)\ n\ (\alpha n)^{1/2}\ ACD^{1/2} v^{1/2}$$

Controlled potential coulometry of DECATH was performed in divided cell filled with CH_3CN-0.1 M $LiClO_4$ using Pt-gauze anode (3 x 5 cm), graphite cathode and SCE. Into 35 ml of analyte DECATH (22 mg, 0.071 mmol) and 2,6-lutidine (38 mg, 0.35 mmol) were added. The potential was increased gradually from 0.5 to 0.6 V vs. SCE. The cyclic voltammograms (GCE, 50 mV/s) were recorded during the electrolysis and the amount of charge was monitored by built-in digital coulometer.

Acknowledgment

We thank Dr. Dean Harman and Mr. Stanley Kolis for preliminary cyclic voltametric measurements and Mr. Kim Harich, VPI&SU, for the HRMS and high molecular weight mass spectra.

References

(1) Noble, R. L. *Biochem. Cell Biol.*, **1990**, *68*, 1344-1351; Gerzon, K. in *Anticancer Agents Based on Natural Product Models*, Cassady, J. M.; Douros, J. D., editors Academic Press, New York, 1980.

(2) Lu, M. C. in Foye, W. D. editor, Cancer Chemotherapeutic Agents, Am. Chem. Soc., 1995, pp 350-353.

(3) Johnson, S. A.; Harper, P.; Hortobogyi, G. N.; Pouillart, P., *Cancer Treat. Rev.*, **1996**, *22*, 127-142.

(4) Reviewed by Pearce, H. L., *The Alkaloids*, **1990**, *37*, 145-204.

(5) Reviewed by Potier, P.; *J. Nat. Prod.*, **1980**, *43*, 72-85. Kutney, J. P., *Nat. Prod. Rept.*, **1990**, 85-103; Kutney, J. P., *Synlett*, **1991**, 11-19; Kutney, J. P., *Acc. Chem. Res.*, **1993**, *26*, 559-566.

(6) Reviewed by Kuehne, M. E.; Marko, I., *The Alkaloids*, **1990**, *37*, 77-131; Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P., *J. Am. Chem. Soc.*, **1992**, *114*, 10232-10245.

(7) (a) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836-4842; (b) Sundberg, R. J.; Cherney, R. J. *J. Org. Chem.* **1990**, *55*, 6028-6037; (c) Sundberg, R. J.; Amat, M.; Fernando, A. M. *J. Org. Chem.* **1987**, *52*, 3151-3159; (d) Sundberg, R. J.; Gadamasetti, K. G. *Tetrahedron*, **1991**, *47*, 5673-5680.

(8) Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1980**, *45*, 3382-3387.

(9) Hamada, T.; Nishida, A.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 140-145.

(10) Szantay, C.; Keve, T.; Bölcskei, H.; Acs, T. *Tetrahedron Lett.* **1983**, *24*, 5539-5542; Szantay, C.; Bölcskei, H.; Gacs-Baitz, E. *Tetrahedron* **1990**, *46*, 1711-1732.

(11) Szantay, C.; Bölcskei, H.; Gacs-Baitz, E.; Keve, T. *Tetrahedron* **1990**, *46*, 1687-1710.

(12) Biswas, K. M.; Jackson, A. H. *Tetrahedron* **1968**, *24*, 1145-1162.

(13) Methyl 2-(1-phenysulfonyl)indole-3-propenoate was prepared by low temperature addition of 3-lithio-1-phenylsulfonylindole to methyl pyruvate, followed by dehydration with Burgess reagent.

(14) Raucher, S.; Bray, G. L. *J. Org. Chem.* **1985**, *50*, 3237-3239; Raucher, S.; Bray, B. L.; Lawrence, R. F. *J. Am. Chem. Soc.* **1987**, *109*, 442-446.

(15) (a) Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P., *J. Am. Chem. Soc.*, **1976**, *98*, 7017-7024; (b) Kutney, J. P.; Choi, L. S. L.; Nakano, J.; Tsukamoto, H.; McHugh, M.; Boulet, C. A., *Heterocycles*, **1988**, *27*, 1845-1853.

(16) (a) Goodbody, A. E.; Endo, T.; Vukovic, J.; Kutney, J. P.; Choi, L. S.; Misawa, M., *Planta Medica*, **1988**, *54*, 210-214; (b) Kutney, J. P.; Vukovic, J.; Goodbody, A. E.; Misawa, M., *Tetrahedron*, **1988**, *44*, 325-331; (c) Tan, M.; Sakamoto, N.; Hata, E.; Ishitoku, T.; Kihara, N., *Eur. Pat. Appl Ep* 354 778, **1990**; *Chem. Abstr.*, **1990**, *113*, 66635; (d) Szantay, C., Jr.; Balazs, J.; Bolcskei, J.; Szantay, C., *Tetrahedron*, **1991**, *47*, 1265-1274; (e) Sakamoto, N.; Tan, H.; Hata, E.; Kihara, N.; Jpn. Kokai Tokkyo Koho JP 0341,081; *Chem. Abstr.*, **1991**, *115*, 50074.

(17) Photochemical: Huhtikangas, A.; Pennanen, S.; Lounasmaa, M.; **1989**, PCT Int. WO89 12 056 *Chem. Abstr.*, **1990**, *112*, 198,880; Pennanen, S.; Huhtikangas, *A.,Photochem. Photobiol.*, **1990**, *51*, 515-518; Hirata, K.; Duangteraprecha, S.; Morihara, E.; Honda, M.; Akagi, T.; Nakae, M.; Katayama, M.; Miyamoto, K., *Biotech. Lett.*, **1997**, *19*, 53-57; Duangteraprecha, S.; Hirato, K.; Morihara, E.; Nakae, M.; Katayama, H.; Honda, M.; Miyamoto, K.; *J. Ferment. Bioeng.*, **1997**, *83*, 227.

(18) Electrochemical: Tabakovic, I.; Gunic, E.; Juranic, I., *J. Org. Chem.*, **1997**, *62*, 947-952.

(19) Enzymatic: Misawa, M.; Endo, T.; Goodbody, A.; Vukovic, J.; Chapple, C.; Choi, L.; Kutney, J. P., *Phytochemistry*, **1988**, *27*, 1355-1359; Kutney, J. P.; Boulet, C. A.; Choi, L. S. L.; Gustowski, W.; McHugh, M.; Nakano, J.; Nikaido, T.; Tsukamoto, H.; Hewitt, G. M.; Suen, R.; *Heterocycles*, **1988**, *27*, 613-620; Kutney, J. P.; Boulet, C. A.; Choi, L. S. L.; Gustowski, W.; McHugh, M.; Nakano, J.; Nikaido, T.; Tsukamoto, H.; Hewitt, G. M.; Suen, R., *Heterocycles*, **1988**, *27*, 621-628; Endo, T.; Goodbody, A.; Vukovic, J.; Misawa, M., *Phytochemistry*, **1988**, *27*, 2147-2149.

(20) Andriamialasoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P.; Blandon, P., *Can. J. Chem.*, **1979**, *57*, 2572-2577;

(21) 5,6-Homodeethylcatharanthine is recovered after attempted Potier coupling with vindoline. Use of $NaBD_4$ reductive workup indicates a mixture of 3-4 and 4-5 elimination; Cherney, R. J. Ph.D. Thesis, University of Virginia, 1990.

(22) Mangeney, P.; Costa, R.; Langlois, N.; Potier, P., *Compte rendu Acad. Sci., Ser. C.*, **1977**,701-703;

Andriamialisoa, R. Z.; Langlois, Y.; Langlois, N.; Potier, P.; *Compte rendu Acad. Sci., Ser. C.*, 1977, 284, 751-754; Honma, Y.; Ban, Y., *Tetrahedron Lett.*, 1978, 155-158.

(23) Sundberg, R. J.; Gadamasetti, K.; Hunt, P. J., *Tetrahedron*, 1992, *48*, 277-296.

(24) When vindoline was omitted, reaction under Potier conditions led to an unstable material characterized by a triplet at 5.6 ppm. Solvolysis of the reaction mixture in methanol resulted in small amounts of the aldehydes *E*-**3a** and *Z*-**3a**. Chromatography of the neutralized reaction mixture led to somewhat unstable compound with the apparent composition $C_{21}H_{26}NO_4$ which had incorporated an ethoxy group. The instability of this material has precluded a definitive structural assignment. Many features of the spectrum are consistent with epoxidation at C15-C20 and C16-C21 cleavage with an ethoxy substituent at C21.

(25) None of the published reports on catharanthine-vindoline coupling by Fe^{3+} (ref 16) describe the behavior of catharanthine alone.

(26) Gueritte, F.; Langlois, N.; Langlois, Y.; Sundberg, R. J.; Bloom, J. D., *J. Org. Chem.*, 1981, *46*, 5393-5395.

(27) Raucher, S.; Bray, B. L.; Lawrence, R. F., *J. Am. Chem. Soc.*, 1987, *109*, 442-446.

(28) Tabakovic, I.; Gunic, E.; Gasic, M. J., *J. Chem. Soc., Perkin Trans. 2*, 1996, 2741-2745.

(29) Roffia, S.; Conciallini, V.; Paradisi, C.; Meran, F.; Vianello, E., *J. Electroanal. Chem.*, 1991, *302*, 115-129; Maran, F., *J. Am. Chem. Soc.*, 1993, *115*, 6557-6563.

(30) Tabakovic, I.; Tabakovic, K., *Tetrahedron Lett.*, 1996, *37*, 3659-3662.

(31) Kondo, T.; Matsuda, T.; Funae, Y. *Jpn Kokai Tokkyo Koho JP61 3645 Chem. Abstr.* 1987, *106*, 17912d.

(32) Prepared from methyl acrylate following the method of Ho, T.-L.; Gupta, B. G. B.; Olah, G. A. *Synthesis* 1977, 676-677.

(33) Moody, C. J.; Rahimtoola, K. F. *J. Chem. Soc. Perkin Trans. 1* 1990, 673-679.

(34) Marvel, C. S.; Dec, J.; Cooke, H. G., Jr.; Cowan, J. C. *J. Am. Chem. Soc.* 1940, *62*, 3495-3498.

(35) This procedure differs from that of Szantay et.al (ref. 16d) in not including one equivalent of HCl. The measured pH of the reaction mixtures was near 2.

(36) Nicholson, R. S.; Shain, I., *Anal. Chem.*, 1964, *36*, 706-723.

(37) Bard, A. J.; Faulkner, L. R., *Electrochemical Methods, Fundamentals and Applications*, Wiley: New York, 1980, p. 222.