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Total Synthesis of Vinblastine, Vincristine, Related Natural Products, and Key Structural Analogues

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Abstract: Full details of the development of a direct coupling of catharanthine with vindoline to provide vinblastine are described along with key mechanistic and labeling studies. Following an Fe(III)-promoted coupling reaction initiated by generation of a presumed catharanthine radical cation that undergoes a subsequent oxidative fragmentation and diastereoselective coupling with vindoline, addition of the resulting reaction mixture to an Fe(III)−$NaBH_4$/air solution leads to oxidation of the C15′−C20′ double bond and reduction of the intermediate iminium ion directly providing vinblastine (40−43%) and leurosidine (20−23%), its naturally occurring C20′ alcohol isomer. The yield of coupled products, which exclusively possess the natural C16′ stereochemistry, approaches or exceeds 80% and the combined yield of the isomeric C20′ alcohols is >60%. Preliminary studies of Fe(III)−$NaBH_4$/air oxidation reaction illustrate a generalizable trisubstituted olefin scope, identify alternatives to O_2 trap at the oxidized carbon, provide a unique entry into C20′ functionalized vinblastines, and afford initial insights into the observed C20′ diastereoselectivity. The first disclosure of the use of *exo*-catharanthine proceeding through $\Delta^{19',20'}$-anhydrovinblastine in such coupling reactions is also detailed with identical stereochemical consequences. Incorporating either a catharanthine *N*-methyl group or a vindoline *N*-formyl group precludes Fe(III)-promoted coupling, whereas the removal of the potentially key C16 methoxy group of vindoline does not adversely impact the coupling efficiency. Extension of these studies provided a total synthesis of vincristine (**2**) via *N*-desmethylvinblastine (**36**, also a natural product), 16-desmethoxyvinblastine (**44**) and 4-desacetoxy-16-desmethoxyvinblastine (**47**) both of which we can now suggest are likely natural products produced by *C. roseus*, desacetylvinblastine (**62**) and 4-desacetoxyvinblastine (**59**), as well as a series of key analogues bearing systematic modifications in the vindoline subunit. Their biological evaluation provided additional insights into the key functionality within the vindoline subunit contributing to the activity and sets the foundation on which further, more deep-seated changes in the structures of **1** and **2** will be explored in future studies.

Introduction

Vinblastine (**1**)[1] and vincristine (**2**) are the most widely recognized members of the class of bisindole alkaloids as a result of their clinical use as antitumor drugs (Figure 1, Velban or Velbe and Oncovin, respectively). Originally they were isolated in trace quantities (0.00025% of dry leaf weight for vinblastine) from the leaves of *Catharanthus roseus* (L.) G. Don,[2] and their biological properties were among the first to be shown to arise from inhibition of microtubule formation and mitosis that today is still regarded as one of the more successful targets for cancer therapeutic intervention.[3]

In addition to being among the first natural products whose structures were determined by X-ray crystallography, they were also among the first for which X-ray analysis of a heavy atom derivative was used to establish their absolute configuration.[4] Both vinblastine and vincristine possess the identical velbanamine upper subunit and nearly identical vindoline-derived lower subunits differing only in the dihydroindole *N*-substituent. Despite this small structural difference, vinblastine and vincristine differ in their antitumor properties and dose-limiting toxicities.[1,3] Two additional semisynthetic vinca alkaloids, vindesine (**3**, Eldesine)[5] and vinorelbine (**4**, Navelbine)[6] have

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10.1021/ja809842b CCC: $40.75

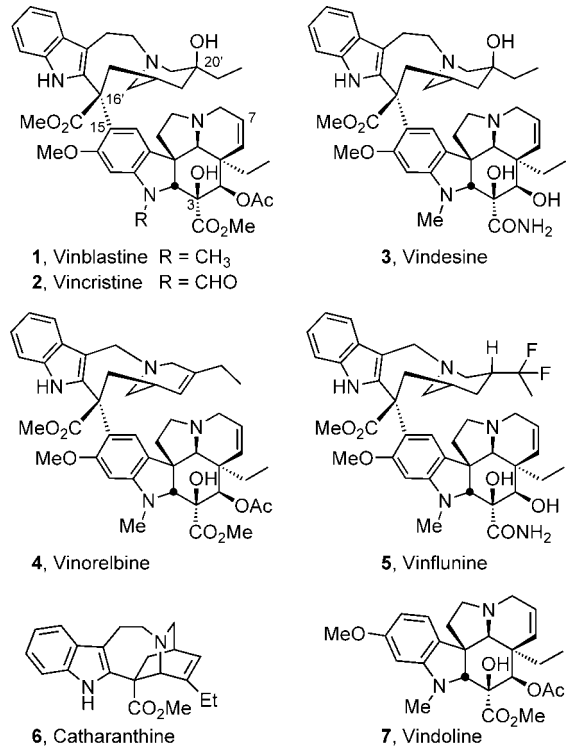

Figure 1. Natural products and related clinical drugs.

been developed as antitumor drugs, and a third, vinflunine (**5**),[7] is in late-stage clinical trials in Europe. Notably, the latter two derivatives incorporate a ring-contracted norvelbanamine upper subunit.

Vincristine (**2**) is used in combination therapy to treat acute leukemias and lymphomas and constitutes an important component of the regime that has been so successful in treating childhood leukemias. Vinblastine (**1**) is often used in combination to treat bladder and breast cancers and is an integral part of the curative treatment regime for Hodgkin's disease. Vinorelbine was approved for use in Europe (1991) and the U.S. (1995) for the treatment of non-small-cell lung cancer and vindesine has been approved for the treatment of melanoma. Neurotoxicity (vincristine) or myelosuppression (vinblastine) are the main side effects of administration and neutropenia is the principal dose-limiting toxicity of the vinca alkaloids, but recovery occurs following treatment. However, the major limitation to the continued use of the vinca alkaloids is the emergence of drug resistance derived principally from overexpression of phosphoglycoprotein (Pgp), an efflux pump that transports many of the major drugs out of the cell. In fact, vinblastine represents one of the most studied prototypical substrates for Pgp efflux responsible for multidrug resistance (MDR). Thus, in addition to identifying vinblastine and vincristine analogues that may address the current dose-limiting toxicities, the development of a modified vinca alkaloid that is not a substrate for Pgp efflux and is efficacious against MDR tumors would constitute a major advance. Additionally, the emerging evidence that the vinca alkaloids also possess antiangiogenic activity that may contribute to their in vivo antitumor activity, especially in combination with other drugs, may provide additional future clinical applications.[8]

Due to the pharmaceutical importance and low natural abundance of vinblastine and vincristine, *C. roseus* has become one of the most extensively studied medicinal plants serving as a model for biotechnological studies of plant secondary metabolism. Their biosynthesis involves the participation of at least 35 intermediates, 30 enzymes, 30 biosynthetic and 2 regulatory genes, and 7 intra- and intercellular compartments.[9] Presently, the clinical supplies of **1** and related drugs are derived from natural sources. Fortunately, the doses are so small that the production amounts are manageable even with the trace natural abundance of **1** (0.01%) or **2** (0.0003%) in the source plants. Nonetheless, the effort required even for this limited quantity suggests that an efficient synthetic approach might provide a viable alternative. Even the development of an effective coupling protocol starting with the more abundant naturally occurring (+)-catharanthine (**6**)[10] and (−)-vindoline (**7**)[2,10] may supplant the direct use of plant produced vinblastine or vincristine. Interestingly, only *C. roseus* produces catharanthine and does so with an absolute configuration enantiomeric with structurally related alkaloids also found in *C. roseus* and related alkaloids found in nature. More significantly, an effective synthetic approach would provide access to analogues that incorporate deep-seated structural changes that have not yet been explored.[3,11] Typically, it has been semisynthetic derivatives of the natural products that have been examined, restricting the structural sites and opportunities to improve on the properties of **1** or **2**.

As a consequence, a number of pioneering studies have defined methods for coupling the lower half, vindoline (**7**), with appropriate precursors to the upper velbanamine subunit. These include the seminal Potier[12] and Kutney[13] disclosures of a coupling protocol enlisting a Polonovski reaction of catharanthine *N*-oxide (**8**) in which its embedded olefin controls the regioselectivity and coupling efficiency of the resulting iminium ion and necessarily provides anhydrovinblastine (**9**), Scheme 1. Conducting the reaction at low temperature was found to

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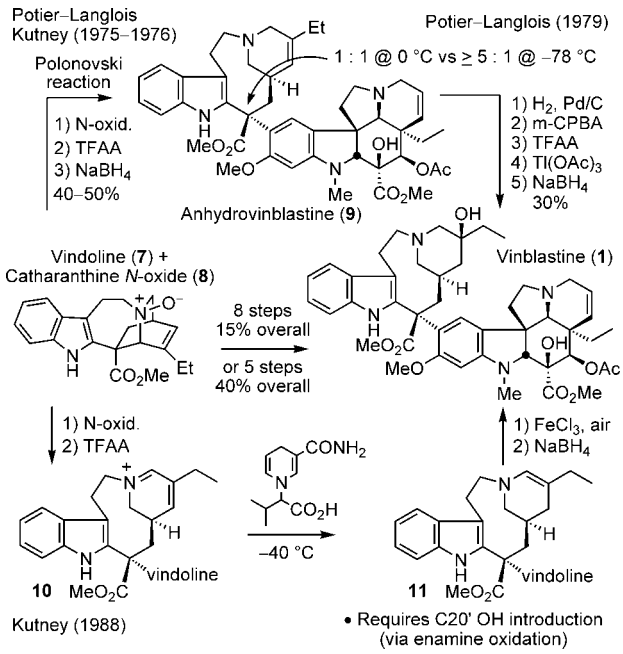
(13) (a) Kutney, J. P.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Heterocycles* **1975**, *3*, 639. (b) Kutney, J. P.; Hibino, T.; Jahngen, E.; Okutani, T.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Helv. Chim. Acta* **1976**, *59*, 2858.

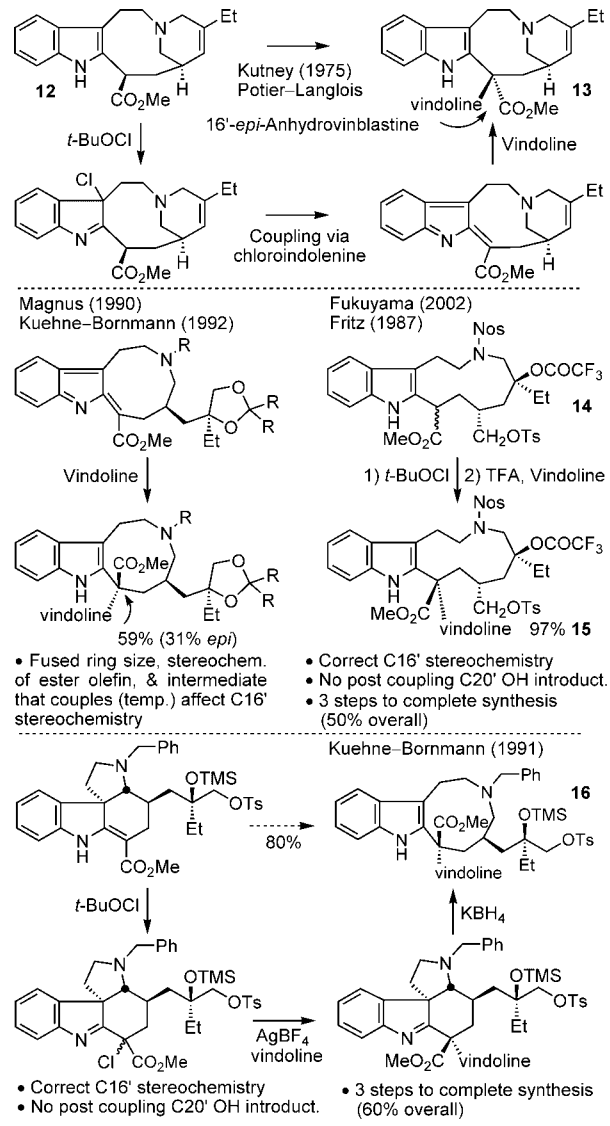
Scheme 1



improve the C16′ coupling diastereoselectivity (>5:1 at −78 °C vs 1:1 at 0 °C),[11] and the subsequent conversion of anhydrovinblastine to vinblastine was addressed by conversion to[14] or with direct generation[15] of the enamine **11** that in turn was oxidized to the C20′ alcohol. This indirect conversion of anhydrovinblastine to vinblastine via the enamine was developed as a result of the preferential α versus β face delivery of reagents to the $\Delta^{15',20'}$-double bond and the competitive reactivity of **9** toward electrophilic reagents required of most olefin oxidation methods. The resulting overall conversions, requiring eight[14] or five[15] steps, range from 10% to 40%.

Alternative approaches enlisting chloroindolenine intermediates derived from indole C3 electrophilic chlorination of precursors to the velbanamine subunit were slower to develop. Following the disclosures that carbomethoxycleaveamine (**12**) couples with vindoline to provide the epimeric C16′ diastereomer **13**,[12,16] both Magnus[17] and Kuehne-Bornmann[18] described protocols that predominantly[17] or exclusively[18] provide the correct C16′ diastereomer, Scheme 2. These enlist velbanamine precursors that proceed through larger indole-fused ring systems or those lacking the velbanamine piperidine requiring postcoupling assemblage of the intact upper subunit. The most effective of these approaches detailed by Kuehne[18] requires four steps postcoupling that proceeded in ca. 60% overall yield. Most

Scheme 2



recently and based on key observations of Fritz,[19] Fukuyama disclosed a diastereoselective coupling of an even more advanced and larger ring velbanamine precursor **14** incorporating the C20′ alcohol permitting access to **1** in 4 steps and ca. 50% overall yield.[20]

Herein, we report the use of a single-step biomimetic coupling of catharanthine (**6**) and vindoline (**7**) to directly provide vinblastine in yields competitive with the best of the past protocols. Not only was this used to extend our 11-step total synthesis of natural (−)- and *ent*-(+)-vindoline[21] to a 12-step total synthesis of natural (+)- and *ent*-(−)-vinblastine, but we also report the application of this modified coupling protocol

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(20) (a) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137. (b) Kuboyama, T.; Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11966. (c) Miyazaki, T.; Yokoshima, S.; Simizu, S.; Osada, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 4737.
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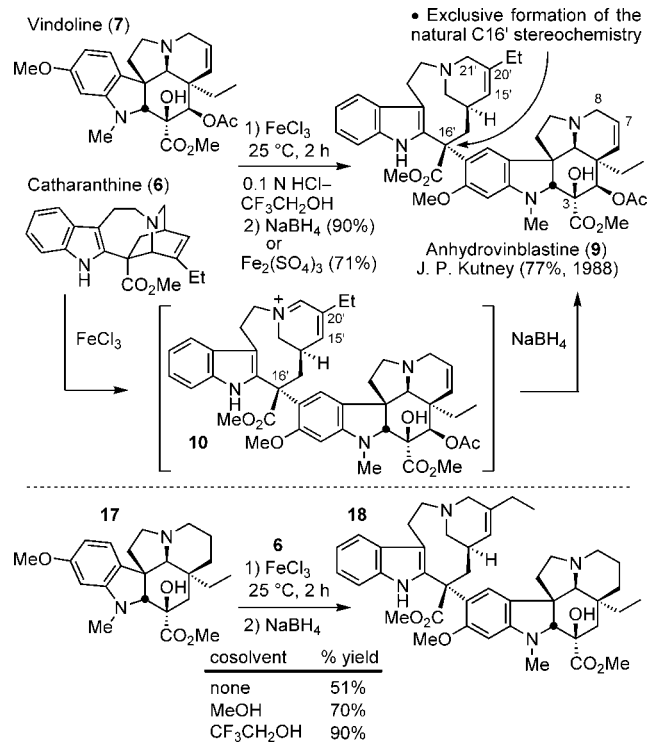
to the total synthesis of vincristine (**2**) and a systematic series of vinblastine analogues, many of which constitute even more minor naturally occurring constituents of the periwinkle *C. roseus* than **1** itself. These analogues constitute a key series in which a single feature in the lower vindoline subunit has been altered, and the results of their examination provide the foundation on which our future studies will be based. In the course of these studies, we conducted detailed mechanistic and labeling studies of the Fe(III)-coupling reaction responsible for formation of the critical C16′ stereocenter, as well as the subsequent low-valent iron-mediated oxidation reaction utilized for C20′ hydroxylation. We also report initial studies on the extension of the oxidation protocol for the introduction of alternative C20′ functionality.

Results and Discussion

With the completion of a first-generation total synthesis of vindoline that was extended to a series of related analogues,[21] we have begun examining protocols for their incorporation into vinblastine and its analogues. In these studies, we found that modification of the direct Fe(III)-promoted biomimetic coupling between catharanthine and vindoline first described by Kutney[22] to produce anhydrovinblastine (**9**) and modification of a subsequent Fe(III)-based oxidation procedure described by Sakamoto[23] can provide vinblastine in a single step in conversions competitive with those of the multistep protocols.[24] Our investigations began with an examination of the Kutney coupling protocol for the generation of anhydrovinblastine.

Coupling of Catharanthine and Vindoline. Anhydrovinblastine (**9**) is itself a naturally occurring vinca alkaloid first demonstrated in biosynthetic labeling studies[25] in *C. roseus* and later by its extraction from the plant.[26] Not only is it an important intermediate in the synthesis of the natural vinca alkaloids but, as the most accessible product from the coupling of vindoline and catharanthine, it is also the semisynthetic precursor to the two non-naturally occurring drugs vinorelbine (**4**) and vinflunine (**5**). Using improved conditions for a coupling first disclosed by Kutney,[22] treatment of a mixture of catharanthine (**6**, 0.022 M) and vindoline (**7**, 0.022 M) with $FeCl_3$ (5 equiv, 23 °C), presumably generating the catharanthine amine radical cation which undergoes a subsequent oxidative fragmentation, leads to biomimetic coupling providing the iminium ion **10** exclusively possessing the natural C16′ stereochemistry, Scheme 3. Reduction with $NaBH_4$ produces anhydrovinblastine (**9**) in superb conversion (90%) provided CF_3CH_2OH, which solubilizes the reactants,[24] is used as a cosolvent with the aqueous 0.1 N HCl

Scheme 3



reaction solution.[27] Although this cosolvent effect provides what might appear to be only a modest improvement for vindoline itself (90% vs 77%),[22,27] this modification is much more significant with a representative less-soluble vindoline analogue **17** that was examined at the same time, Scheme 3. The use of MeOH as a cosolvent provided a homogeneous reaction solution and improved the conversions, but it also provided the MeOH addition product with catharanthine and appeared to promote the self-coupling of **7** or **17** arising from their oxidation. Replacing MeOH with the non-nucleophilic cosolvent CF_3CH_2OH provided a homogeneous reaction mixture, superb conversions with both vindoline (90%) and **17** (90%), and little or no self-coupling products derived from either **7** or **17**. Finally, conducting the reaction under Ar in degassed solvents appeared to subtly improve the conversions (by 5−10%) although reactions conducted without such precautions still proceed superbly.

The additional feature of this reaction that we wish to report is that $Fe_2(SO_4)_3$ (5 equiv) also effects the coupling of vindoline with catharanthine to provide anhydrovinblastine in good yields (71%) under the same conditions. Although this unoptimized conversion is not yet as superb as that observed with $FeCl_3$, it represents an Fe(III) reagent that, unlike $FeCl_3$, effectively supports the subsequent oxidation of anhydrovinblastine to vinblastine without further additives. Moreover and unlike $Fe_2(ox)_3$ (below), which supports the anhydrovinblastine oxidation but not the vindoline/catharanthine coupling, $Fe_2(SO_4)_3$ is an iron reagent capable of supporting both the initial coupling and subsequent oxidation.

As first observed by Sundberg,[27b] *N*-methylcatharanthine (**19**) fails to couple with vindoline upon treatment with $FeCl_3$ even

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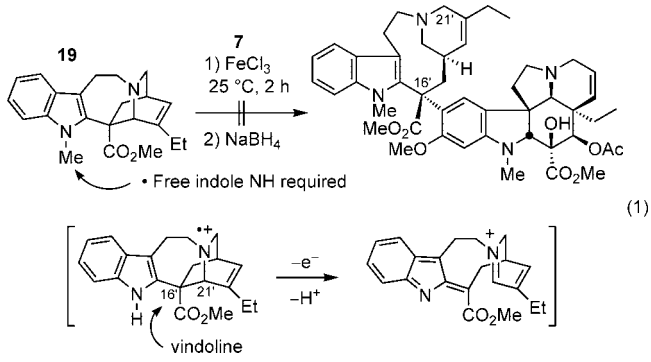
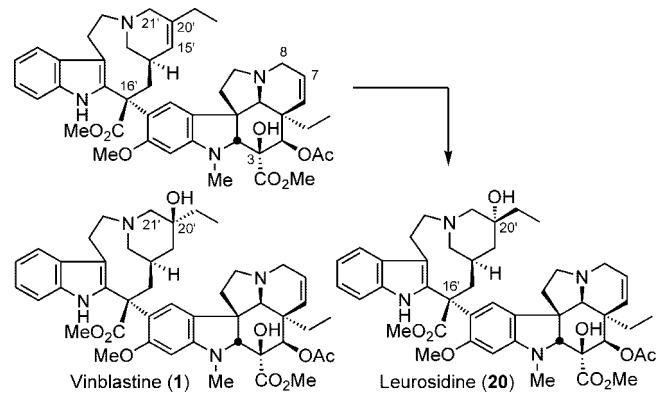
under our modified reaction conditions, eq 1. Although Sundberg observed that **19** is consumed (but not coupled) with vindoline present and is recovered unchanged in absence of vindoline, we observed the consumption of **19** whether vindoline was present or not. Analogous observations have been made with Potier's Polonovski reaction with *N*-methyl catharanthine *N*-oxide that also failed to initiate coupling with vindoline leading simply to fragmentation.[28] The implication of this requirement for a free indole NH has been discussed in detail by others[28] and suggests azabenzfulvene participation in the catharanthine fragmentation and its subsequent coupling with vindoline. However, and unlike the Polonovski-based coupling protocol of Potier, the Fe(III)-promoted catharanthine oxidative fragmentation proceeds with exclusive formation of the natural C16′ stereochemistry even at 25 °C, which corresponds to clean inversion of the stereochemistry at the reacting C16′ center of the C16′−C21′ bond undergoing cleavage. Although at odds with invoking an azabenzfulvene intermediate and not offered as a mechanistic rationale, this stereochemical outcome follows expectations of vindoline attack at C16′ concurrent with fragmentation.



(1)

Oxidation of Anhydrovinblastine to Vinblastine. Although oxidation of the $\Delta^{15',20'}$-double bond of anhydrovinblastine has been observed and explored with a full range of oxidants including air (O_2),[29,30] none do so preferentially from the β-face. Most such efforts provide the corresponding α-epoxide (leurosine), and none provide vinblastine or its naturally occurring C20′ alcohol isomer leurosidine (**20**) in appreciable amounts. The exception to this is the oxidation protocol of Sakamoto.[23] This oxidation entails the direct Fe-mediated ($FeCl_3$, 30−500 equiv) conversion of anhydrovinblastine (**9**) to vinblastine and leurosidine in the presence of air (O_2) at 0−25 °C in aqueous buffer containing carboxylic acid additives (e.g., ammonium oxalate) upon addition of a reducing agent including $NaBH_4$ (30 min). As a prelude to our more detailed studies combining an Fe(III)-promoted oxidation of anhydrovinblastine with the Kutney Fe(III)-mediated coupling of vindoline and catharanthine, we briefly examined this reaction, Scheme 4. Simply submitting anhydrovinblastine (**9**) to the oxidation conditions (30 equiv $FeCl_3$, air, 0 °C, 1 h; 20 equiv $NaBH_4$) in the Kutney 0.1 N HCl/glycine buffer only provided trace amounts of vinblastine. By using ammonium oxalate (60−120 equiv) as an additive, oxidation with $FeCl_3$ (30−60 equiv)/$NaBH_4$ (20−50 equiv) in our 0.1 N HCl/CF_3CH_2OH solvent system at 0 °C under progressively dilute conditions (0.22 mM) provided improved conversions (ca. 35−40%) being derived in part from the increasing O_2 content that is limited by its solubility (concentration). Finally, by utilizing $Fe_2(ox)_3$ under heterogeneous (30 equiv) or homogeneous (10 equiv, see below) conditions in place of the $FeCl_3$-additive combinations, superb conversion to vinblastine (50%) and leurosidine (20%) was achieved. Notably, no reaction is observed in the absence of the initiating reductant ($NaBH_4$). Further, $NaBH_4$ proved superior to the limited number of alternative reagents examined (e.g., $NaCNBH_3$, $LiBH_4$, $NaBH(OAc)_3$, BH_3, Bu_3SnH), olefin reduction is observed in the absence of air (O_2), other conventional oxidants (e.g., H_2O_2, *t*-BuOOH) failed to support the reaction, and the reaction proceeds directly from **9** to **1**/**20** without the intermediacy of the isomerized enamine **11**[31] or oxidized iminium ion **10**[32] (see labeling studies). Moreover, and as detailed in subsequent studies, this trisubstituted olefin oxidation reaction (C20′−OH derived from O_2) is not unique to anhydrovinblastine and does not require the allylic amine. Interestingly and although not investigated in detail, the seemingly analogous Mukaiyama Co(II)-mediated olefin oxidation ($Co(acac)_2$, O_2, $PhSiH_3$) failed to provide either vinblastine or leurosidine from **9**.[33]

Scheme 4

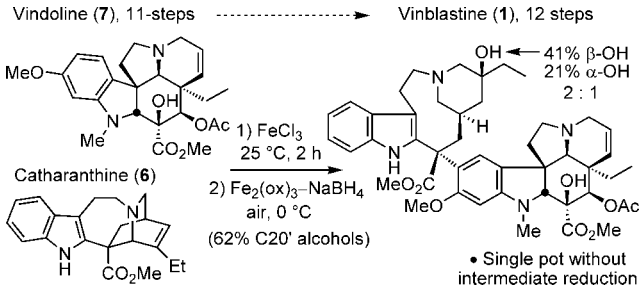


Conditions	Result	
1) $FeCl_3$ (30 equiv) air, 0 °C, 0.1 N HCl–glycine buffer 2) $NaBH_4$ (20 equiv), 0 °C, 30 min	trace **1**	trace **20**
1) $FeCl_3$ (30 equiv), $(CO_2NH_4)_2$ (60 equiv) air, 0 °C, 0.1 N HCl–CF_3CH_2OH 2) $NaBH_4$ (20 equiv), 0 °C, 30 min	35–40% **1**	14–18% **20**
1) $Fe_2(ox)_3$ (30 equiv, suspension) air, 0 °C, 0.1 N HCl–CF_3CH_2OH 2) $NaBH_4$ (20 equiv), 0 °C, 30 min	50% **1**	20% **20**

One-Step Coupling and Oxidation Reaction: Total Synthesis of Natural (+)-Vinblastine and *ent*-(−)-Vinblastine. The preceding studies set the stage for combining the initial Fe(III)-promoted vindoline/catharanthine coupling reaction with the subsequent Fe(III)-based oxidation reaction to directly provide vinblastine (**1**) in a single step, Scheme 5.[23] Thus, $FeCl_3$ (5 equiv) mediated coupling of vinblastine with catharanthine using

(28) Sundberg, R. J.; Gadamasetti, K.; Hunt, P. J. *Tetrahedron* **1992**, *48*, 277.
(29) (a) Langlois, N.; Potier, P. *J. Chem. Soc., Chem. Commun.* **1978**, 102. (b) Langlois, N.; Potier, P. *J. Chem. Soc., Chem. Commun.* **1979**, 582.
(30) For example, see: (a) Kutney, J. P.; Balsevich, J.; Bokelman, G. H.; Hibino, T.; Honda, T.; Itoh, I.; Ratcliffe, A. H.; Worth, B. R. *Can. J. Chem.* **1978**, *56*, 62.
(31) Kutney, J. P.; Choi, L. S. L.; Nakano, J.; Tsukamoto, H.; McHugh, M.; Boulet, C. A. *Heterocycles* **1988**, *27*, 1845.
(32) (a) Kutney, J. P.; Choi, L. S. L.; Nakano, J.; Tsukamoto, H. *Heterocycles* **1988**, *27*, 1827. (b) Kutney, J. P.; Choi, L. S. L.; Nakano, J.; Tsukamoto, H. *Heterocycles* **1988**, *27*, 1837. (c) Mukaiyama, T.; Isayama, S.; Inoki, S.; Kato, K.; Yamada, T.; Takai, T. *Chem. Lett.* **1989**, 449.
(33) (a) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 1071. (b) Tokuyasa, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. *Org. Lett.* **2002**, *4*, 3595.

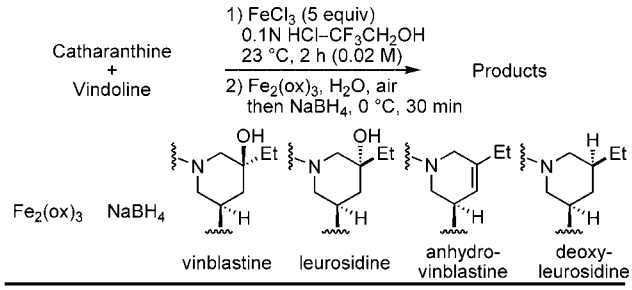
Scheme 5



our solvent modification on the Kutney procedure (0.1 N HCl/CF_3CH_2OH) *without reductive workup* is followed by addition of the reaction mixture containing the iminium ion **10** to a second Fe(III) solution (soluble $Fe_2(ox)_3$, 10 equiv) cooled to 0 °C and saturated with air. Subsequent addition of $NaBH_4$ (20 equiv) initiates both reduction of the intermediate iminium ion and selective oxidation of the $\Delta^{15',20'}$-double bond with installation of the C20′ alcohol to provide vinblastine (**1**, 41%), its naturally occurring C20′ alcohol isomer leurosidine[2] (**20**, 21%), along with anhydrovinblastine (**9**, 10%). The yield of identifiable coupled material exceeds 80−90% with the combined yield of C20′ alcohols being 62−69% (2:1 β/α). This one step coupling reaction was conducted to provide natural (+)-vinblastine, as well as with synthetic *ent*-(+)-vindoline[21] and *ent*-(−)-catharanthine to provide *ent*-(−)-vinblastine ($[\alpha]_D^{23}$ −38 (*c* 0.05, $CHCl_3$)).

One of the most important features to emerge from the optimization efforts, which included a more detailed accounting of all characterizable products, was the effect of utilizing solubilized $Fe_2(ox)_3$ in the second oxidation reaction. In the course of our early work and the optimization of the second stage of the reaction (Supporting Information, Table S1), $Fe_2(ox)_3$ was found to be more effective than most iron salts for promoting the olefin oxidation with installation of the C20′ alcohol. Like the Sakamato protocol,[23] the stoichiometry was high, resulting in heterogeneous reaction conditions where not all the iron salt was soluble at the onset of the reaction (addition of $NaBH_4$). Completely solubilizing the initial $Fe_2(ox)_3$ solution by stirring the suspended salt solution for an extended period (2 h) before the onset of the reaction (air bubbling for 10 min, then addition of $NaBH_4$) resulted in a much more efficient and equally effective oxidation reaction, Figure 2. In fact, the use of solubilized $Fe_2(ox)_3$ (30 equiv) led to over oxidation of vinblastine, a result that was improved by reducing the amount of $Fe_2(ox)_3$ (10 equiv). Reoptimization of the amount of added $NaBH_4$ to initiate the reaction (20 equiv) and a re-examination of the reaction concentration (0.2 mM) which insures an adequate supply of dissolved O_2 provided a superb and highly reproducible single step coupling protocol.

Although we did not conduct an exhaustive survey of Fe(III) salts, both Fe(III) citrate and FeF_3 (at 60 equiv, 40 equiv $NaBH_4$) failed to support the oxidation reaction (both insoluble), $Fe(NO_3)_3$ provided only a modest level of oxidation, whereas $Fe_2(SO_4)_3$ proved nearly as effective as $Fe_2(ox)_3$. In addition and because of its solubility properties (soluble in H_2O/EtOH), the use of $Fe_2(SO_4)_3$ permitted the exploration of additional cosolvents, Figure 3. Here, the use of even 1:1 H_2O/EtOH did not shut down the oxidation reaction although the conversion to vinblastine was more modest (27% vs 40%). These observations indicate that studies of alternative Fe(III) reagents, as well as the incorporation of additional reaction cosolvents, especially



$Fe_2(ox)_3$	$NaBH_4$	vinblastine	leurosidine	anhydro-vinblastine	deoxy-leurosidine
30 equiv (suspended)	20 equiv	41%	21%	19%	9%
30 equiv (soluble)	20 equiv	24%	20%	20%	12%
15 equiv (soluble)	20 equiv	40%	24%	7%	6%
10 equiv (soluble)	20 equiv	41–40%	21–20%	4–13%	4–8%
5 equiv (soluble)	20 equiv	32%	17%	16%	6%
10 equiv (soluble)	100 equiv	31%	19%	27%	7%
10 equiv (soluble)	40 equiv	35%	17%	10%	6%
10 equiv (soluble)	30 equiv	43%	26%	12%	10%
10 equiv (soluble)	10 equiv	16%	10%	36%	5%
10 equiv (soluble)	20 equiv (0.45 mM)	39%	19%	14%	10%
10 equiv (soluble)	20 equiv (0.9 mM)	27%	16%	19%	14%
10 equiv (soluble)	10 equiv (0.45 mM)	19%	12%	41%	5%

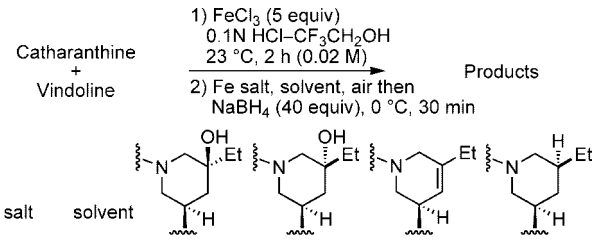
Oxidation reaction run saturated with air at 0.2 mM unless stated otherwise.

Figure 2. Optimization of use of $Fe_2(ox)_3$.

those that readily dissolve O_2, might serve to further improve the overall conversions. Significantly, the Fe(II) reagent $FeSO_4$ failed to support the oxidation reaction. Additionally, small improvements in the yield (lutidine, 43% **1**; DBU, 44% **1**) or diastereoselectivity (2,2′-bipyridine, 3:1 **1/20**) have been observed when the oxidation with $Fe_2(ox)_3$ is run in the presence of an organic base suggesting further optimization may still be possible (Supporting Information, Table S2).

Finally, we were able to demonstrate that a single Fe(III) reagent ($Fe_2(SO_4)_3$) is capable of supporting both the initial coupling and subsequent oxidation. Although limited optimization efforts were conducted revealing that systematic reductions in the amount of $Fe_2(SO_4)_3$ and $NaBH_4$ led to progressively lower conversions, our initial trials do suggest conditions likely could be developed that may entail simply sequential addition of air (10 min bubbling) and $NaBH_4$ following the 2 h coupling reaction, Figure 4.

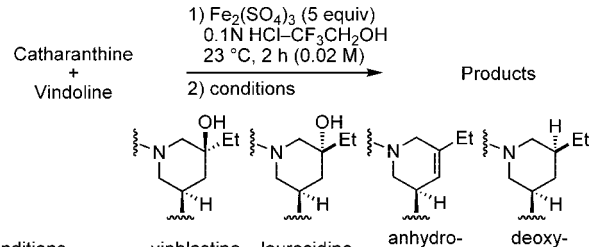
Labeling Studies. In order to clarify the steps involved in the coupling and oxidation conversions to vinblastine, labeling experiments ($NaBD_4$, D_2O, $^{18}O_2$) were conducted to distinguish between otherwise attractive mechanistic possibilities, Scheme 6. By utilizing MS, and ^1H and ^2H NMR characterization of the products (Supporting Information), the number, site, and stereochemistry of deuterium incorporation obtained from use of $NaBD_4$ in the coupling preparation of anhydrovinblastine indicate one D incorporation at α-C21′ consistent with the report of Kutney in his analysis of the Polonovski coupling,[32a] a clean key and diagnostic single D incorporation at α-C15′ in the oxidation of anhydrovinblastine to vinblastine, and clean D



Fe salt	solvent	vinblastine	leurosidine	anhydro-vinblastine	deoxy-leurosidine
none (ammonium oxalate)	H_2O	–	–	70%	–
Fe(III)citrate 60 equiv	H_2O	–	–	87%	–
FeF_3 60 equiv	H_2O	–	–	65%	–
$Fe(NO_3)_3$ 60 equiv	H_2O	10%	17%	63%	nd
$FeCl_3$ 60 equiv	H_2O	21%	21%	22%	nd
$Fe_2(SO_4)_3$ 60 equiv	H_2O	39%	22%	33%	nd
$Fe_2(SO_4)_3$ 60 equiv	H_2O–EtOH (1:1 v/v)	27%	22%	25%	nd
$Fe_2(SO_4)_3$ 60 equiv	H_2O–EtOH (1:9 v/v)	12%	20%	40%	nd
$FeSO_4$ 60 equiv	H_2O	–	–	72%	–

Reactions run saturated with air at 0.2 mM unless specified otherwise.

Figure 3. Survey of additional iron reagents.



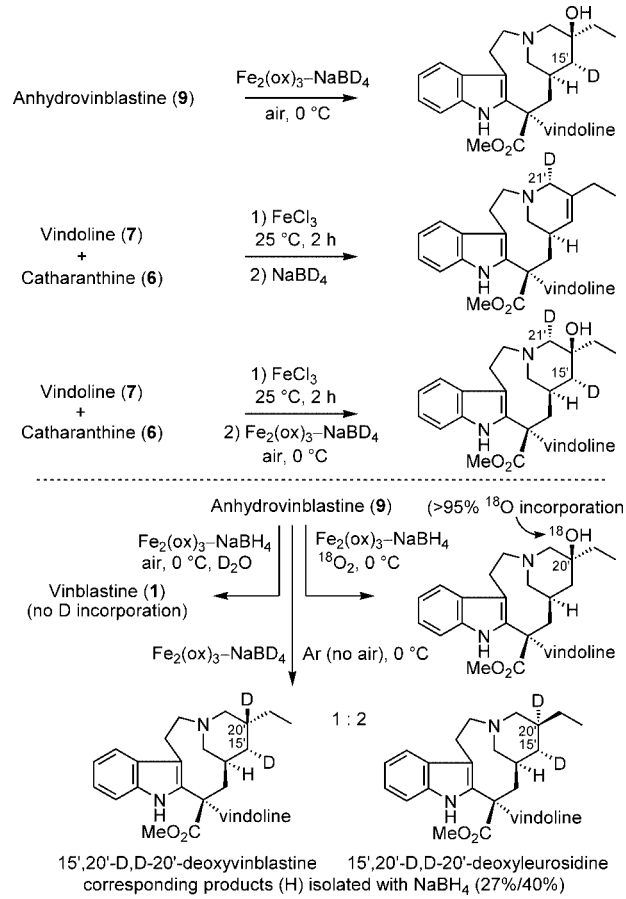
Conditions	vinblastine	leurosidine	anhydro-vinblastine	deoxy-leurosidine
$NaBH_4$ (5 equiv)	–	–	71%	nd
1) air (1 h) 2) $NaBH_4$ (5 equiv) 0 °C, 30 min	11%	15%	40%	nd
1) $Fe_2(SO_4)_3$ (60 equiv) air (10 min) 2) $NaBH_4$ (40 equiv) 0 °C, 30 min	33%	23% (+ over oxidation products)	21%	nd

Reactions run saturated with air at 0.2 mM unless specified otherwise.

Figure 4. Single-step coupling with $Fe_2(SO_4)_3$.

incorporation at each α-C15′ and α-C21′ in the combined coupling and oxidation reaction. In the oxidation of anhydrovinblastine to vinblastine, reactions run in D_2O led to no deuterium incorporation, $^{18}O_2$ labeling studies indicate the C20′ alcohol oxygen originates with O_2 (oxidation reaction, >95% by MS) and not solvent water (hydration reaction), and reactions run in the absence of O_2 lead to selective reduction of the $\Delta^{15',20'}$-double bond providing C20′-deoxyvinblastine and its diastereomer C20′-deoxyleurosidine (1:1.5−2). This latter reduction diastereoselectivity (1:2) is reversed from that of the 2:1 diastereoselectivity observed in the oxidation reaction providing **1** and **20**, and the use of $NaBD_4$ indicates clean deuterium (two D) incorporation with one D at only α-C15′ and C20′. Although it is conceivable that the C20′ oxidation arises from 1,4-reduction of iminium ion **10** followed by enamine **11** oxidation, the labeling studies for the oxidation of anhydrovinblastine (**9**) to

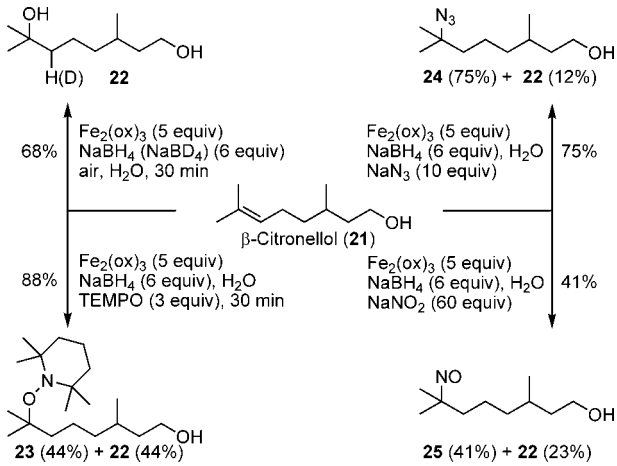
Scheme 6



1 (50%) and its C20′-isomer leurosidine (15−20%) under the Fe(III)−$NaBH_4$/O_2 conditions indicate that it can do so without the intermediacy of **10** indicating this is not necessary to achieve C20′ hydroxylation. Thus, the labeling studies ($NaBD_4$) not only rule out the reoxidation to and intermediacy of iminium ion **10** in the conversion of anhydrovinblastine (**9**) to vinblastine, but they also rule out an Fe-catalyzed isomerization of **9** to enamine **11** and its resulting oxidation (no C21′ D incorporation). Additionally, reactions that should promote a 1,4-reduction of iminium ion **10** (e.g., $NaCNBH_3$)[14] result in subsequent enamine **11** protonation and reduction, not C20′ oxidation providing a mixture of anhydrovinblastine (**9**, 48% from 1,2-reduction) and 20′-deoxyleurosidine (31% from 1,4-reduction). Finally, subjection of either 20′-deoxyvinblastine or 20′-deoxyleurosidine to the oxidation conditions does not produce either vinblastine or leurosidine.

Without belaboring a discussion of all mechanistic possibilities, the labeling studies are most consistent with the oxidation of anhydrovinblastine to vinblastine by an Fe-mediated hydrogen atom radical addition to the trisubstituted $\Delta^{15',20'}$-olefin initiated by $NaBH_4$ treatment of an appropriate Fe(III) salt followed by reaction of the resulting carbon centered tertiary radical with O_2 and subsequent reduction of the resulting hydroperoxide. In the one step coupling and subsequent oxidative conversion of vindoline and catharanthine to vinblastine, the $NaBH_4$ serves to both reduce the iminium ion **10** to anhydrovinblastine (**9**) and as the controlled source of the Fe-promoted hydrogen atom radical generation for initiation of the olefin oxidation. Further supporting these interpretations are the observations below including the demonstration that the Fe(III)−$NaBH_4$(air) oxida-

Scheme 7

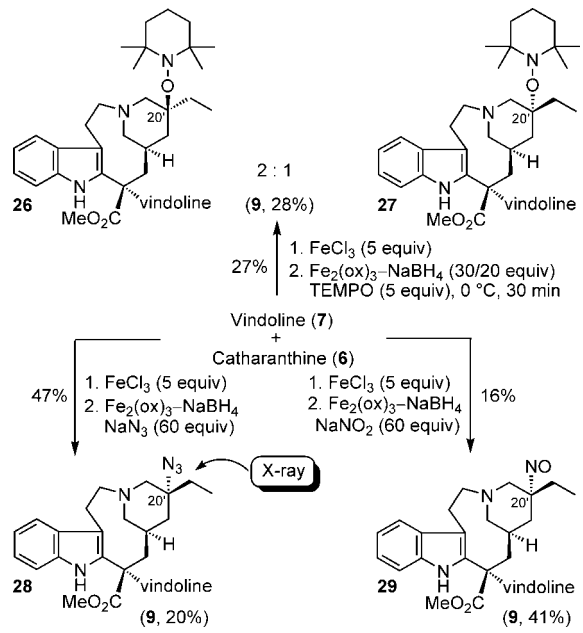


tion reaction is not unique to substrates bearing the tertiary allylic amine. Finally, it is worth noting that the chemistry derived from the $NaBH_4$ reduction of Fe(III) salts is complex,[34] presumably distinct from the behavior of the well-characterized hydridocarbonyliron complexes,[35] and little precedent is available to draw mechanistic insights from. However, it is notable that the radical-mediated oxidation of an olefin (styrene) by a phthalocyanine Fe(III)−$NaBH_4$ system in the presence of O_2,[36] Fe(II)- or Fe(III)-mediated alkene and alkyne reductions enlisting $LiAlH_4$ in the absence of O_2, and $FeCl_3$−$NaBH_4$ mediated sulfoxide and β-amino-enone reductions have been reported.[37]

Scope of the Fe(III)−$NaBH_4$ Mediated Reactions. As part of the mechanistic probe of the Fe(III)−$NaBH_4$(air) oxidation reaction, we examined the generality of the reaction with β-citronellol (**21**), a water-soluble substrate bearing a trisubstituted double bond lacking the complexity of anhydrovinblastine and its tertiary allylic amine. Subjection of **21** to the oxidation conditions cleanly provided the tertiary alcohol **22** (68%) in good yield requiring less reagent (5 equiv of $Fe_2(ox)_3$, 6 equiv $NaBH_4$) than enlisted for the oxidation of anhydrovinblastine, and the use of $NaBD_4$ provided the analogous single deuterium incorporation, Scheme 7. Inclusion of TEMPO (3 equiv) in the reaction mixture afforded the TEMPO adduct **23** in good yield (44%) along with **22** (44%), providing a superb combined yield of oxidation products (88%) and confirming that a radical trap is effectively incorporated at the oxidized carbon. Alternatively and without efforts at optimization, the inclusion of NaN_3[38] (10 equiv) in a reaction run under Ar provided **24** (75%) in high yield whereas the use of $NaNO_2$[39] (60 equiv) afforded the nitroso adduct **25** (41%). Thus, not only is the Fe(III)−$NaBH_4$(air) oxidation reaction general for additional substrates containing a trisubstituted olefin, but alternatives to O_2 may be used to functionalize the oxidized carbon.

Total Synthesis of C20′-Functionalized Vinblastine Analogues. These latter studies, in addition to providing key mechanistic insights into the anhydrovinblastine oxidation reaction, also introduce a unique opportunity for the synthesis of vinblastine analogues bearing modified C20′ functionality.[40] To date, such studies have been limited to semisynthetic modifications of vinblastine itself and largely restricted to *O*-acylation (OH→OCOR), alcohol elimination and subsequent olefin reduction (OH→H) or acid/superacid catalyzed-additions including the reaction utilized to prepare the corresponding C20′ acetamido vinblastine analogue (OH→NHAc).[41] Thus, starting with either anhydrovinblastine (**9**) or, more significantly, the coupling of vindoline and catharanthine followed by in situ generation and functionalization of **9**, vinblastine analogues containing additional C20′ functionality may be accessed. As a demonstration of this potential and the scope of the Fe(III)−$NaBH_4$ alkene addition reactions, the C20′ derivatives **26**−**29** bearing TEMPO, azido, and nitroso C20′ substituents were prepared, Scheme 8.

Scheme 8



Impressively, these were generated starting from vindoline and catharanthine using the one-pot coupling and subsequent in situ oxidation protocol even at a stage that the procedure was not yet optimized and directly provided **26**−**29**. Notably, the TEMPO trap did not alter or improve the intrinsic 2:1 diastereoselectivity favoring the vinblastine versus leurosidine C20′ stereochemistry for an oxygen substituent, the azide of **28** was introduced with remarkable efficiency (47% overall) directly from vindoline/catharanthine even without optimization, and both the azide and nitroso groups were introduced providing exclusively the leurosidine versus vinblastine C20′ stereochemistry. In each instance, the C20′ stereochemical assignments were made on the basis of diagnostic ^{1}H NMR chemical shifts of three distinct signals: 3′-Hβ (br t), 6′-Hβ (dd), and 17′-Hβ (d). Each proton exhibits an unusual and distinct chemical shift, and

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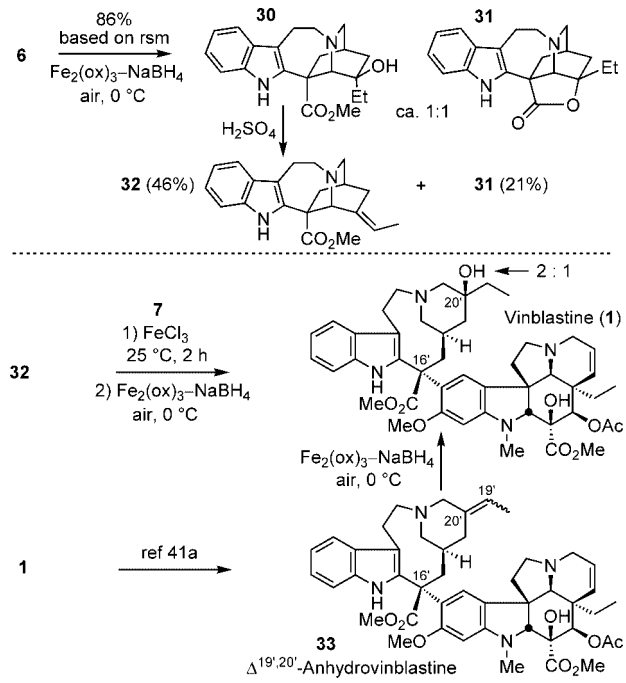
(38) Snider, B. B.; Duvall, J. R. *Org. Lett.* **2004**, *6*, 1265.
(39) Kato, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2948.
(40) The single-crystal X-ray structure of **28** establishing its structure and relative stereochemistry was derived from off-white crystals obtained from EtOAc and has been deposited with the Cambridge Crystallographic Data Centre (CCDC 713670).
(41) (a) Miller, J. C.; Gutowski, G. E.; Poore, G. A.; Boder, G. B. *J. Med. Chem.* **1977**, *20*, 409. (b) Miller, J. C.; Gutowski, G. E. Ger Patent 2753791-19780608 (*Chem. Abstr.* **1978**, *89*, 129778). (c) Gerzon, K.; Miller, J. C. Eur. Patent 55602 (*Chem. Abstr.* **1982**, *97*, 163310). (d) Review of superacid functionalization: Duflos, A.; Kruczynski, A.; Barret, J.-M. *Curr. Med. Chem.-Anti-Cancer Agents* **2002**, *2*, 55.

Scheme 9



each is further downfield for the vinblastine versus leurosidine C20′ stereochemistry (Supporting Information, Table S3). Concerned that this correlation, as strong as it appeared, might not prove accurate for establishing the C20′ stereochemistry with **28** and **29** where only a single isomer was observed, we unambiguously established the structure and stereochemistry for azide **28** by single-crystal X-ray analysis.[40] Not only did this confirm the structure and assigned C20′ stereochemistry of **28**, but it also served to reaffirm the C16′ stereochemistry set in the initial coupling reaction between vindoline and catharanthine. Finally and not surprisingly, azide **28** was also produced in a comparable conversion by treatment of anhydrovinblastine (**9**) with $Fe_2(ox)_3$−$NaBH_4$ (10 equiv/30 equiv) in the presence of NaN_3 (60 equiv). No doubt, many other C20′ functionalized derivatives may be accessed by using this approach and these will be investigated in due course.

Coupling of *exo*-Catharanthine versus Catharanthine: $\Delta^{19',20'}$-Anhydrovinblastine and its Oxidation to Vinblastine. As an alternative to coupling catharanthine with vindoline and in efforts to improve the diastereoselectivity of the C20′ alcohol introduction, we prepared and examined the substrate **32**, Scheme 9. This catharanthine isomer incorporates an exocyclic versus endocyclic double bond, but it is still positioned to provide the necessary control of regioselectivity for the oxidative fragmentation of **32** and its radical cation required for coupling with vindoline. The question was would this impact the diastereoselectivity of the olefin oxidation reaction enlisted for direct introduction of the C20′ alcohol. Without optimization, substrate **32** was prepared from catharanthine (**6**) using our $Fe_2(ox)_3$/$NaBH_4$(air) conditions for direct oxidation of the trisubstituted olefin providing a near 1:1 mixture of the tertiary alcohol **30** and the lactone **31** derived from the isomeric alcohol. Subsequent acid-catalyzed elimination of water provided the desired substrate **32** (46%) and additional lactone **31** (21%). The direct single-step coupling of **32** with vindoline (**7**) with in situ oxidation of the C20′ center proceeded with a diastereoselectivity that was not distinguishable from the use of catharanthine itself (single natural C16′ diastereomer, 2:1 C20′ alcohol diastereomers) and in unoptimized conversions that approached (30−32% vinblastine, 16−20% leurosidine), but did not surpass those optimized for **6**. Similarly, oxidation of the intermediate $\Delta^{19',20'}$-anhydrovinblastine (**33**)[41a] provided the same 2:1 mixture of C20′ alcohol diastereomers when exposed to the $Fe_2(ox)_3$/$NaBH_4$(air) oxidation conditions. Nonetheless and despite the disappointment that the use of **32** or **33** did not alter this 2:1 diastereoselectivity, their success provides synthetic access to vinblastine or its analogues through a coupling that has not been previously examined, provides an alternative synthesis of $\Delta^{19',20'}$-anhydrovinblastine for semisynthetic modifications, and suggests that both **9** and **33** or **32** and **6** proceed through a common intermediate in the oxidation to provide vinblastine/leurosidine.

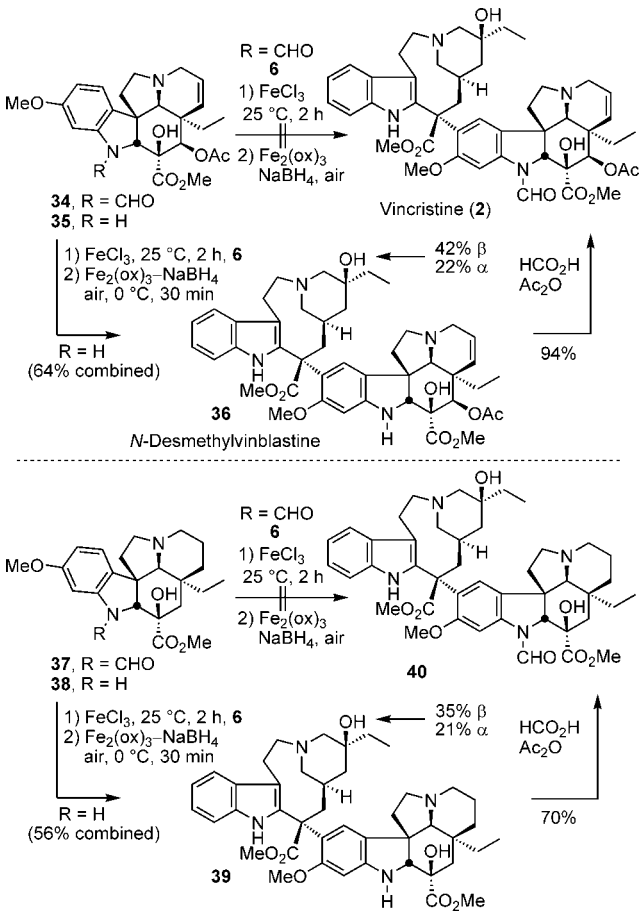
Total Synthesis of (+)-Vincristine and (+)-1-Desmethylvinblastine. The remainder of our efforts focused on defining the scope of the Fe(III)-promoted coupling reaction and its extension to a series of key analogues bearing modifications in the lower vindoline subunit. The most significant of these is vincristine (**2**) bearing a *N*-formyl group in the lower subunit that necessarily impacts its nucleophilic reactivity in the coupling with the electrophilically activated catharanthine. Although it is well-known that *N*-formylvindoline (**30**) fails to participate in the Polonovski reaction with catharanthine *N*-oxide (**8**),[1] we are unaware of reports of its reactivity in the Fe(III)-promoted coupling reaction. Therefore, both **34** and a simplified model **37** (Supporting Information)[42] were examined and both failed to couple with catharanthine under our modified coupling conditions, Scheme 10. Thus, an indirect approach enlisting the coupling of (−)-*N*-desmethylvindoline (**35**)[21,43−45] with catharanthine (**6**) to first provide *N*-desmethylvinblastine (**36**), a natural product in its own right and useful naturally occurring precursor to vincristine,[2] and its subsequent formylation was adopted. Thus, both **35** and **38** reacted effectively with catharanthine (**6**) under our one-step protocol for both coupling and subsequent oxidation to directly provide **36** (42%) or **39** (35%) and their corresponding 20′ alcohol diastereomers (22% and 21%, respectively). Formylation of **36** and **39** (HCO_2H, Ac_2O, 23 °C, 2 h) provided vincristine (**2**, 94%) and **40** (70%) in good overall conversions.

Coupling of (−)-Vindorosine (Desmethoxyvindoline) and Analogues: Total Synthesis of (−)-16-Desmethoxyvinblastine and Related Analogues. We also viewed the coupling of (−)-vindorosine (**41**) with catharanthine (**6**) as an additional test of the scope of the Fe(III)-promoted coupling reaction and one that also provides the key vinblastine analogue **44** not yet examined. Not only would this further define the scope of the chemistry achievable using the methodology, but the subsequent evaluation of **44** would define the importance and potential role of the vinblastine C16 methoxy substituent. Moreover and as a result of our earlier synthetic efforts that provided the natural product (−)-vindorosine[46] and a range of naturally occurring (**42**)[21] or synthetic (**43**) analogues,[47] both **42** and **43** were also

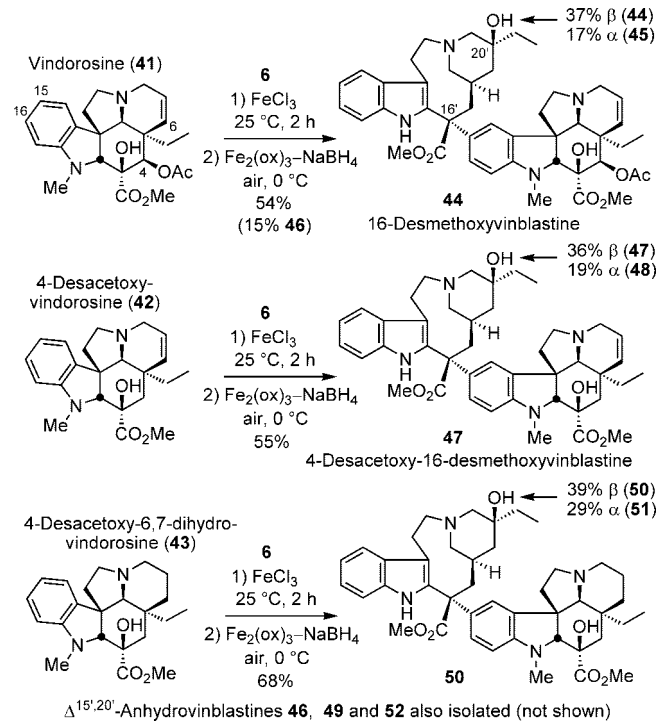
(42) The substrates **33** and **34** were prepared utilizing the tandem [4 + 2]/[3 + 2] 1,3,4-oxadiazole cycloaddition cascade as detailed in the Supporting Information with a chromatographic resolution.

(43) Bolcskei, H.; Gacs-Baitz, E.; Szantay, C. *Tetrahedron Lett.* **1989**, *30*, 7245.
(44) Balazs, M.; Szantay, C., Jr.; Bolcskei, H.; Szantay, C. *Tetrahedron Lett.* **1993**, *34*, 4397.
(45) Goodbody, A. E.; Watson, C. D.; Misawa, M. *Chem. Abstr.* **1992**, *116*, 235944.
(46) Elliott, G. I.; Velcicky, J.; Ishikawa, H.; Li, Y.; Boger, D. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 620.

Scheme 10



Scheme 11



available to examine. The former provides access to 4-desacetoxy-16-desmethoxyvinblastine (**47**), which along with **44** we can now suggest likely constitute natural products produced by *C. roseus* awaiting isolation and characterization. Thus, vindorosine (**41**), **42**, and **43** were subjected to the one-step Fe(III)-promoted coupling reaction with catharanthine (**6**) and subsequent $Fe_2(ox)_3-NaBH_4$(air) oxidation reaction to provide the corresponding C16-desmethoxyvinblastine and leurosidine analogues in the ca. 2:1 diastereoselectivity favoring the vinblastine C20′ stereochemistry along with 15−20% of the corresponding anhydrovinblastine analogues **46**, **49**, and **52**, respectively (not shown), Scheme 11.

Thus, removal of the C16 methoxy substituent from vindoline or related substrates does not negatively impact the coupling reaction promoted by Fe(III). This is in contrast to observations made enlisting the Polonovski coupling conducted at 0 °C where the yield was substantially reduced (18% and 81% recovered vindorosine) and only the unnatural C16′ stereochemistry (*R* vs *S*) was observed.[12b] Significantly, **44** and the related bisindole alkaloids exhibited substantially altered spectroscopic (^{1}H NMR) properties. Most notably, the ^{1}H NMR is typically less crisp and the characteristic C17′ and C6′ signals and their chemical shifts diagnostic of the natural C16′ and C20′ stereochemistry for **1** (δ 4.51 and 4.04, respectively) move to higher field (<δ 3.80). These observations suggest that the conformation of **44**−**52** is substantially altered or, more precisely, that they may access many more available conformations consistent with expectations that the presence of the C16 methoxy group restricts rotation about the critical C15−C16′ bond linking the two halves of such molecules. Accordingly and as detailed herein, the removal of this C16 methoxy group results in a substantial, but not complete, loss in cytotoxic potency. Nonetheless, the observation of modest biological activity with the desmethoxyvinblastine derivatives would seem to confirmed that the coupling generates the natural C15−C16′ stereochemistry; an assignment we still regard as tentative as a result of the unusual optical rotations [**46** (−), but **49** and **52** (+) vs **1** and related analogues (+)].

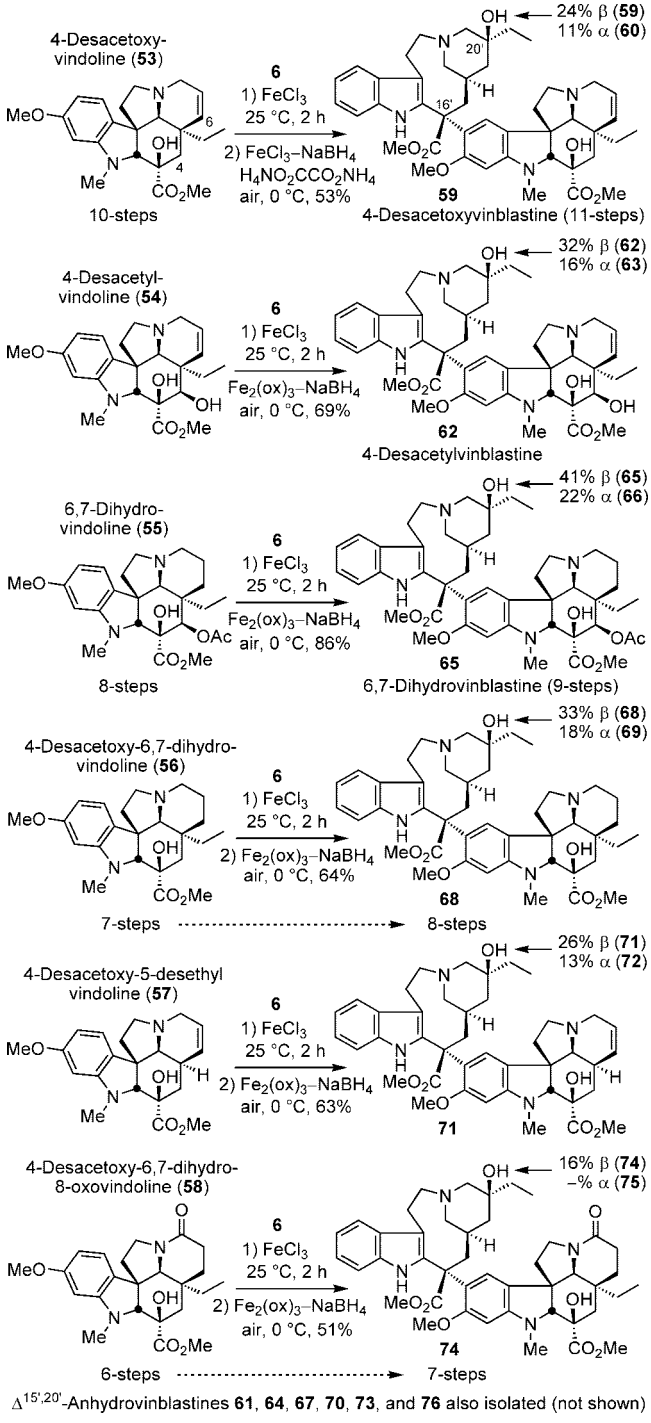
Coupling of Additional Key Analogues of Vindoline: Total Synthesis of (+)-4-Desacetylvinblastine and (+)-4-Desacetoxyvinblastine. As a result of our prior efforts, a series of additional key analogues (**53**−**58**) of vindoline were prepared for incorporation into the corresponding vinblastine analogue, Scheme 12.[21,48] Each constitutes the iterative removal of key substituents found in the vindoline subunit of vinblastine (e.g., C4−Ac, C4−OAc, C5−Et, C6−C7 double bond), at least two (**59** and **62**) constitute natural products in their own right,[2] and their evaluations were expected to continue to help define the individual substituent roles. 4-Desacetylvinblastine (**62**) is the penultimate biosynthetic precursor to **1** and the precursor to a series of potent and efficacious semisynthetic C4 *O*-acyl vinblastine derivatives.[49] 4-Desacetoxyvinblastine (**59**) is its immediate biosynthetic precursor and constitutes an even more minor (10-fold) naturally occurring bisindole alkaloid than **1**, which itself is found in trace amounts (≤0.00025% of dry leaf weight). It has been reported to possess equally efficacious, but less potent, antitumor activity compared to vinblastine and was not pursued due to its even lower natural abundance.[5] Because these studies were conducted at an early stage of our efforts even before we had the opportunity to examine the single step

(47) Yuan, Z.; Ishikawa, H.; Boger, D. L. *Org. Lett.* **2005**, *7*, 741.

(48) Ishikawa, H.; Boger, D. L. *Heterocycles* **2007**, *72*, 95.

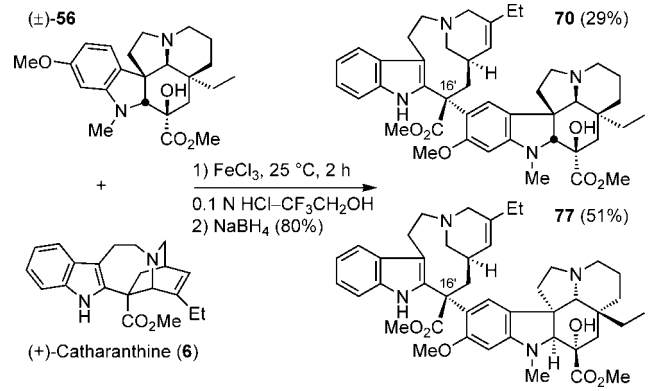
(49) Johnson, I. S.; Hargrove, W. W.; Harris, P. N.; Wright, H. F.; Boder, G. B. *Cancer Res.* **1966**, *26*, 2431.

Scheme 12



coupling and subsequent oxidation reaction in detail, many of the preparations were conducted enlisting our original non optimal oxidation conditions (30 equiv $FeCl_3$, 60 equiv $H_4NCO_2CO_2NH_4$, air, 20 equiv $NaBH_4$, 30 min; see Scheme 4) providing modest conversions by our present standards. Although not evident from the presentation above, the concise syntheses of many of the vindoline analogues [e.g., **56** (7 steps), **58** (6 steps), **55** (8 steps), **53** (10 steps)],[21,46−48] their direct chromatographic resolution, and their single-step incorporation into the corresponding natural product or vinblastine analogue provides a remarkably concise synthetic entry into this class of bisindole antitumor agents (<10 steps) that was inconceivable to us as we began our studies. Not only does this simplify the synthetic access to additional analogues for further study, but it also suggests that a totally synthetic analogue is economically well within reach for use in the clinic.

Scheme 13

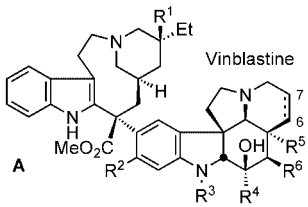


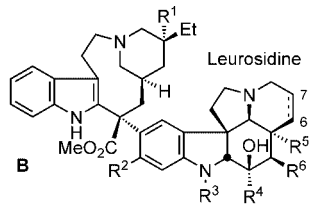
Coupling of (+)-Catharanthine with a Racemic Vindoline Derivative. Sundberg has reported that the Fe(III)-promoted coupling of racemic catharanthine (2 equiv) with natural (−)-vindoline (1 equiv) provided recovered racemic catharanthine (1:1 mixture of enantiomers), indicating that the reaction proceeds without a kinetic diastereoselectivity (resolution) favoring the natural product.[27b] Since the two products were not characterized, we elected to additionally examine this reaction, but using (+)-catharanthine (1 equiv) and the readily available racemic vindoline derivative **56** (2 equiv) with characterization of the resulting anhydrovinblastine derivatives. Interestingly and perhaps remarkably, the Fe(III)-promoted coupling reaction provided **70** (natural, 29%) and **77** (unnatural, 51%) in a 1:1.75 ratio with both products possessing the correct C16′ stereochemistry, but slightly favoring the coupling of the unnatural enantiomer of **56**, Scheme 13. Independently, the natural enantiomer of **56** (90%, Scheme 3) and the unnatural enantiomer of **56** (77%) were coupled with (+)-catharanthine providing **70** and **77**, respectively, confirming the product assignments derived from the coupling of racemic **56**.

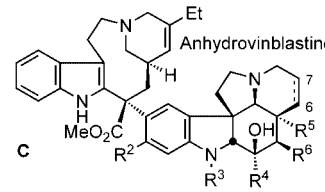
Cytotoxic Activity. The studies detailed herein provided a wide range of analogues of **1** and **2** bearing single point changes in their structures permitting an assessment of their contributions to the cellular activity of the natural products (cytotoxic activity against L1210 and HCT116). Additionally, the analogues were examined for their susceptibility to multidrug resistance (MDR), resulting from overexpression and drug efflux by Pgp using a well-established companion vinblastine resistant cell line (HCT116/VM46).[50] The results of these studies are summarized in Figure 5.

Several of the natural products, their simple derivatives, or analogues have been previously reported,[2,3b,11,14,15,18] but in many instances without establishing their in vitro cytotoxic activity. For those reported (**1**−**3**, **9**, **20**, **33**), the activity compares well with the potency disclosed and many of the overall trends highlight those already recognized: vinblastine > anhydrovinblastine (typically 10-fold) > leurosidine (typically 100-fold) analogue and that the 20′-deoxy derivatives are quite potent. Examination of the analogues derived from the systematic removal of the key vindoline substituents [C4−Ac (equipotent), C4−OAc (10-fold), N1−Me (10-fold), C5−Et (10-

(50) (a) Dumontet, C.; Sikic, B. I. *J. Clin. Oncol.* **1999**, *17*, 1061. (b) Kavallaris, M.; Verrills, N. M.; Hill, B. T. *Drug Res. Updates* **2001**, *4*, 392.







Compound (**A**)	R^1	R^2	R^3	R^4	R^5	R^6	C6/C7	IC_{50} (nM) L1210	HCT116	HCT116/VM46
1 Vinblastine	OH	OMe	Me	CO_2Me	Et	OAc	C=C	5.6	5.0	220
2 Vincristine	OH	OMe	CHO	CO_2Me	Et	OAc	C=C	6.0	6.8	700
- 20'-Deoxyvinblastine	H	OMe	Me	CO_2Me	Et	OAc	C=C	40	40	100
62 4-Desacetylvinblastine	OH	OMe	Me	CO_2Me	Et	OH	C=C	5.8	5.2	480
59 4-Desacetoxyvinblastine	OH	OMe	Me	CO_2Me	Et	H	C=C	58	60	660
65 6,7-Dihydrovinblastine	OH	OMe	Me	CO_2Me	Et	OAc	C–C	570	370	4500
44 16-Desmethoxyvinblastine	OH	H	Me	CO_2Me	Et	OAc	C=C	570	580	3500
36 1-Desmethylvinblastine	OH	OMe	H	CO_2Me	Et	OAc	C=C	70	70	3000
26 20'-Tempo-vinblastine	TEMPO	OMe	Me	CO_2Me	Et	OAc	C=C	4000	3800	5600
71 4-Desacetoxy-5-desethylvinblastine	OH	OMe	Me	CO_2Me	H	H	C=C	610	400	3510
68 4-Desacetoxy-6,7-dihydrovinblastine	OH	OMe	Me	CO_2Me	Et	H	C–C	660	670	4000
40 4-Desacetoxy-6,7-dihydrovincristine	OH	OMe	CHO	CO_2Me	Et	H	C–C	520	480	6000
74 4-Desacetoxy-6,7-dihydro-8-oxovinblastine	OH	OMe	Me	CO_2Me	Et	H	C–C[a]	4600	4700	9600
47 4-Desacetoxy-16-desmethoxyvinblastine	OH	H	Me	CO_2Me	Et	H	C=C	5500	5600	6500
50 4-Desacetoxy-16-desmethoxy-6,7-dihydrovinblastine	OH	H	Me	CO_2Me	Et	H	C–C	>10000	>10000	8800
39 4-Desacetoxy-1-desmethyl-6,7-dihydrovinblastine	OH	OMe	H	CO_2Me	Et	H	C–C	6700	7600	10000
3 Vindesine	OH	OMe	Me	$CONH_2$	Et	OH	C=C	16	7	750
- 6,7-Dihydovindesine	OH	OMe	Me	$CONH_2$	Et	OH	C–C	55	45	1000
- Vindesine Hydrazine	OH	OMe	Me	$CONHNH_2$	Et	OH	C=C	9	6.5	700
Compound (**B**)	R^1	R^2	R^3	R^4	R^5	R^6	C6/C7	L1210	HCT116	HCT116/VM46
20 Leurosidine	OH	OMe	Me	CO_2Me	Et	OAc	C=C	690	620	8300
- 20'-Deoxyleurosidine	H	OMe	Me	CO_2Me	Et	OAc	C=C	460	360	2500
27 20'-Tempo-leurosidine	TEMPO	OMe	Me	CO_2Me	Et	OAc	C=C	600	630	1500
28 20'-Azidoleurosidine	N_3	OMe	Me	CO_2Me	Et	OAc	C=C	560	600	4700
- 20'-Aminoleurosidine	NH_2	OMe	Me	CO_2Me	Et	OAc	C=C	5600	5600	>10000
29 20'-Nitrosoleurosidine	NO	OMe	Me	CO_2Me	Et	OAc	C=C	50	40	2000
63 4-Desacetylleurosidine	OH	OMe	Me	CO_2Me	Et	OH	C=C	6200	4000	>10000
60 4-Desacetoxyleurosidine	OH	OMe	Me	CO_2Me	Et	H	C=C	6000	6400	>10000
66 6,7-Dihydroleurosidine	OH	OMe	Me	CO_2Me	Et	OAc	C–C	6000	6800	>10000
45 16-Desmethoxyleurosidine	OH	H	Me	CO_2Me	Et	OAc	C=C	3700	6600	9100
- 1-Desmethylleurosidine	OH	OMe	H	CO_2Me	Et	OAc	C=C	6000	7000	10000
69 4-Desacetoxy-6,7-dihydroleurosidine	OH	OMe	Me	CO_2Me	Et	H	C–C	6100	6200	8500
48 4-Desacetoxy-16-desmethoxyleurosidine	OH	H	Me	CO_2Me	Et	H	C=C	5600	7500	8700
72 4-Desacetoxy-5-desethylleurosidine	OH	OMe	Me	CO_2Me	H	H	C=C	>10000	>10000	>10000
51 4-Desacetoxy-16-desmethoxy-6,7-dihydroleurosidine	OH	H	Me	CO_2Me	Et	H	C–C	>10000	>10000	>10000
- 4-Desacetoxy-1-desmethyl-6,7-dihydroleurosidine	OH	OMe	H	CO_2Me	Et	H	C–C	>10000	>10000	>10000
- 1-Desmethyl-20'-deoxyleurosidine	H	OMe	H	CO_2Me	Et	OAc	C=C	500	560	3000
Compound (**C**)	R^1	R^2	R^3	R^4	R^5	R^6	C6/C7	L1210	HCT116	HCT116/VM46
9 Anhydrovinblastine	–	OMe	Me	CO_2Me	Et	OAc	C=C	65	75	580
- 4-Desacetylanhydrovinblastine	–	OMe	Me	CO_2Me	Et	OH	C=C	65	65	820
61 4-Desacetoxyanhydrovinblastine	–	OMe	Me	CO_2Me	Et	H	C=C	3900	4700	6000
67 6,7-Dihydroanhydrovinblastine	–	OMe	Me	CO_2Me	Et	OAc	C–C	740	890	3500
46 16-Desmethoxyanhydrovinblastine	–	H	Me	CO_2Me	Et	OAc	C=C	600	700	910
- 1-Desmethylanhydrovinblastine	–	OMe	H	CO_2Me	Et	OAc	C=C	420	430	830
70 4-Desacetoxy-6,7-dihydroanhydro-vinblastine	–	OMe	Me	CO_2Me	Et	H	C–C	5400	5600	5300
73 4-Desacetoxy-5-desethylanhydro-vinblastine	–	OMe	Me	CO_2Me	H	H	C=C	>10000	>10000	>10000
76 4-Desacetoxy-6,7-dihydro-8-oxo-anhydrovinblastine	–	OMe	Me	CO_2Me	Et	H	C–C[a]	>10000	>10000	>10000
49 4-Desacetoxy-16-desmethoxy-anhydrovinblastine	–	H	Me	CO_2Me	Et	H	C=C	5300	7000	7300
52 4-Desacetoxy-16-desmethoxy-6,7-dihydroanhydrovinblastine	–	H	Me	CO_2Me	Et	H	C–C	5500	5800	6300
- 4-Desacetoxy-1-desmethyl-6,7-dihydroanhydrovinblastine	–	OMe	H	CO_2Me	Et	H	C–C	>10000	10000	10000
33 $\Delta^{19',20'}$-Anhydrovinblastine	–	OMe	Me	CO_2Me	Et	OAc	C=C	420	200	5400
Unnatural Enantiomers										
1 *ent*-(–)-Vinblastine (**A**)	OH	OMe	Me	CO_2Me	Et	OAc	C=C	>10000	>10000	>10000
9 *ent*-(–)-Anhydrovinblastine (**C**)	–	OMe	Me	CO_2Me	Et	OAc	C=C	>10000	>10000	>10000
20 *ent*-(–)-Leurosidine (**B**)	OH	OMe	Me	CO_2Me	Et	OAc	C=C	>10000	>10000	>10000
- *ent*-(–)-20'-Deoxyleurosidine (**B**)	H	OMe	Me	CO_2Me	Et	OAc	C=C	>10000	>10000	>10000
77	–	OMe	Me	CO_2Me	Et	H	C–C	5600	4700	6000

[a] 8-oxo derivative

Figure 5. Cytotoxic activity.

fold), C16−OMe (100-fold), C6−C7 double bond (100-fold), C20′−OH (8-fold)] indicate that the C16−OMe and C6−C7 double bond appear to be more important than the C4 or N1 substituents and that the latter sites constitute useful positions for modification or synthetic simplifications (removal) that remain quite potent (e.g., **59**, **62**, **36**, **71**). However, the introduction of more polar functionality at C3 appears to dampen the loss in activity due to such changes (e.g., **3**/6,7-dihydro-**3**, 4−7 fold vs 100-fold for **1**/**65**), suggesting that even the more significant structural simplifications may be tolerated within the appropriate derivatives. The effects of the substituent removal typically are cumulative although they are dampened as the analogues become increasingly less potent. Additionally, the isomeric $\Delta^{19',20'}$-anhydrovinblastine (**33**) proved to be less potent than anhydrovinblastine (**9**, 2−10 fold), the unique 20′-nitrosoleurosidine (**29**, IC_{50} = 40−50 nM) was found to be remarkably potent and the trends established for this series (20′-NO > 20′-H > 20′-N_3 > 20′-TEMPO ≥ 20′-OH > 20′-NH_2) indicate that this is a site rich for modification using the technology detailed herein, the leurosidine 20′-TEMPO derivative (**27**, 3−7 fold) was surprisingly potent and more active than the corresponding vinblastine derivative (**26**), and the unnatural enantiomers examined (**1**, **9**, **20**) were inactive. None of the analogues exhibited substantially improved activity against the resistant cell line HCT116/VM46 indicating they are subject to Pgp efflux although those bearing modification at C20′ (e.g., deoxyvinblastine, anhydrovinblastine) displayed a diminished loss of activity against the resistant cell lines. These observations set the foundation on which further, more deep-seated changes in the structures of **1** and **2** will be explored in future studies.

Conclusions

With the introduction of the intramolecular cascade [4 + 2]/[3 + 2] cycloaddition reaction of 1,3,4-oxadiazoles[51] that is ideal for the assemblage of the functionalized pentacyclic ring system of vindoline and its simpler variants,[21] its extension to the total synthesis of vinblastine, vincristine, related natural products, and key analogues was initiated. Herein we provide full details of the development of a direct coupling of catharanthine with vindoline to provide vinblastine along with key mechanistic and labeling studies. Following an Fe(III)-promoted coupling reaction initiated by generation of a presumed catharanthine radical cation that undergoes a subsequent oxidative fragmentation and diastereoselective coupling with vindoline, addition of the resulting reaction mixture to an Fe(III)−$NaBH_4$/air solution led to oxidation of the C15′−C20′ double bond and reduction of the intermediate iminium ion directly providing vinblastine (40−43%) and leurosidine (20−23%). The yield of coupled products, which exclusively possess the natural C16' stereochemistry, approached or exceeded 80% and the combined yield of the isomeric C20′ alcohols was >60%. Preliminary studies of Fe(III)−$NaBH_4$/air oxidation reaction illustrate a generalizable trisubstituted olefin scope, identified alternatives to O_2 trap at the oxidized carbon, provided a unique entry into C20′ functionalized vinblastines, and afforded initial insights into the observed C20′ diastereoselectivity. The first disclosure of the use of *exo*-catharanthine proceeding through $\Delta^{19',20'}$-anhydrovinblastine in such coupling reactions was also detailed with identical stereochemical consequences. Incorporating either a catharanthine *N*-methyl group or a vindoline *N*-formyl group precluded Fe(III)-mediated coupling, whereas the removal of the C16 methoxy group of vindoline did not adversely impact the coupling efficiency. Extension of these studies provided a total synthesis of vincristine (**2**) via *N*-desmethylvinblastine (**36**, also a natural product), 16-desmethoxyvinblastine (**44**), and 4-desacetoxy-16-desmethoxyvinblastine (**47**) both of which we can now suggest are likely natural products produced by *C. roseus*, desacetylvinblastine (**62**) and 4-desacetoxyvinblastine (**59**), as well as a series of key analogues bearing systematic modifications in the vindoline subunit. Their biological evaluation provide additional insights into the key functionality within the vindoline subunit contributing to the activity and sets the foundation on which further, more deep-seated changes in the structures of **1** and **2** will be explored in future studies.

Acknowledgment. We gratefully acknowledge the financial support of the National Institute of Health (CA115526 and CA042056) and the Skaggs Institute for Chemical Biology. We are also especially grateful to Paul Hellier of Pierre Fabre for the generous gift of vindoline, vindorosine, and catharanthine.

Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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