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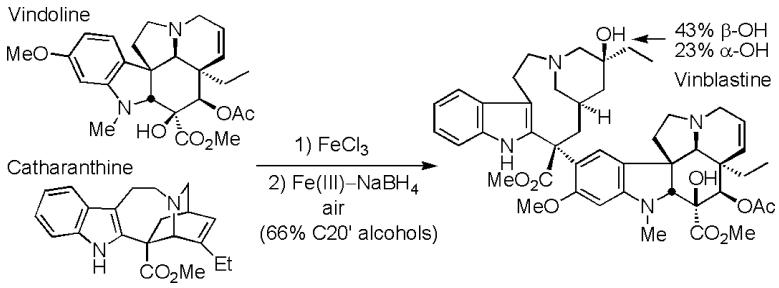

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Direct Coupling of Catharanthine and Vindoline to Provide Vinblastine: Total Synthesis of (+)- and *ent*-(−)-Vinblastine

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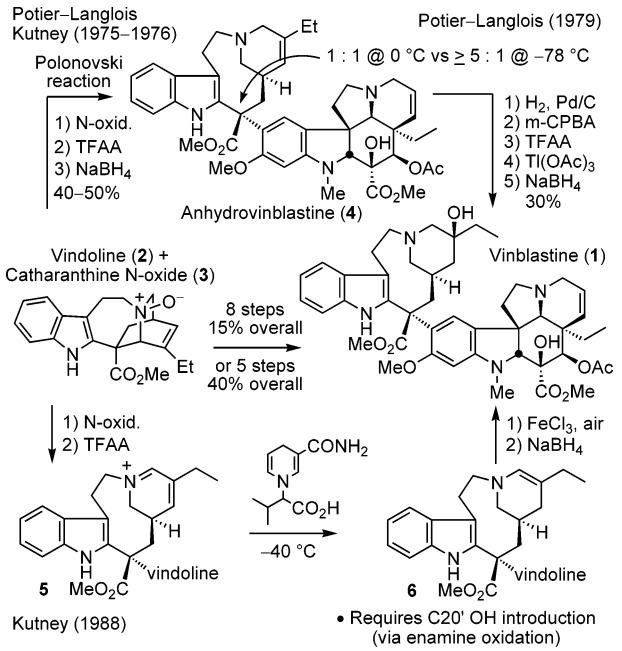
Vinblastine (**1**)[1] is the most widely recognized member of the class of bisindole alkaloids as a result of its clinical use as an antitumor drug. Originally isolated in trace quantities (0.00025% of dry leaf weight) from *Catharanthus roseus* (L.) G. Don,[2] its biological properties were among the 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]

Presently, the clinical supplies of **1** and related drugs[3c] 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**. Nonetheless, the effort required even for this limited quantity suggests that an efficient synthetic approach might provide a viable alternative. More significantly, an effective synthetic approach would provide access to analogues that incorporate deep-seated structural changes not yet explored.[4]

As a consequence, a number of pioneering studies have defined methods for coupling the lower half, vindoline (**2**), with appropriate precursors to the upper velbanamine subunit. These include the seminal Potier[5] and Kutney[6] disclosures of a coupling protocol enlisting a Polonovski reaction of catharanthine *N*-oxide (**3**) in which its embedded olefin controls the regioselectivity and coupling efficiency of the resulting iminium ion and necessarily provides anhydrovinblastine (**4**) (Scheme 1). Conducting the reaction at low temperature was found to improve the C16′ coupling diastereoselectivity (≥5:1 at −78 °C vs 1:1 at 0 °C),[4] and the subsequent conversion of anhydrovinblastine to vinblastine was addressed by conversion to[7] or with direct generation[8] of the enamine **6** which in turn was oxidized to the C20′ alcohol. This indirect conversion of anhydrovinblastine to vinblastine via the enamine was necessitated by the preferential α versus β face delivery of reagents to the $\Delta^{15',20'}$-double bond and the competitive reactivity of **4** toward electrophilic reagents required of most olefin oxidation methods. The resulting overall conversions, requiring eight[7] or five[8] 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 carbomethoxycleavamine (**7**) couples with vindoline to provide the epimeric C16′ diastereomer **8**,[5,9] both Magnus[10] and Kuehne−Bornmann[11] described protocols that predominantly, albeit not exclusively, provide the correct C16′ diastereomer (Scheme 2). These enlist velbanamine precursors with larger indole-fused ring systems requiring post-coupling assemblage of the intact upper subunit. Most recently and on the basis of key observations of Fritz,[12] Fukuyama disclosed a diastereoselective coupling of an even more advanced and larger ring velbanamine precursor **9** incorporating the C20′ alcohol permitting access to **1** in four steps and ca. 50% overall yield.[13]

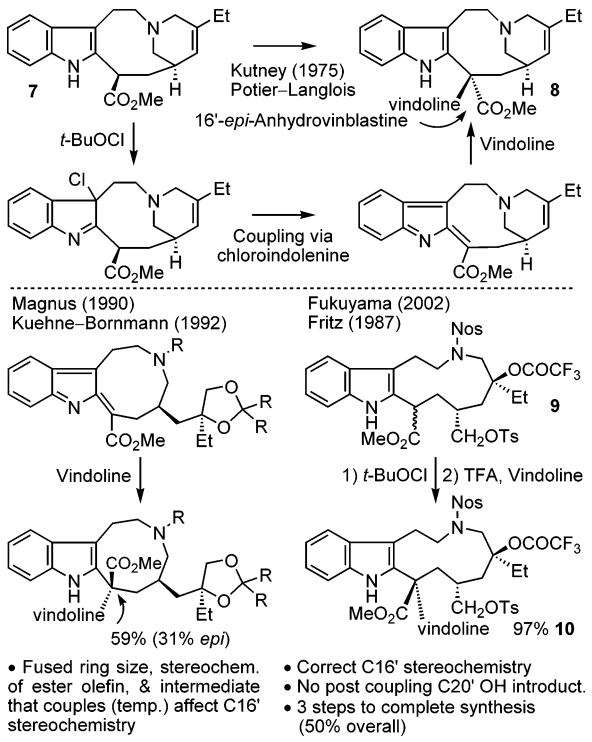
With the completion of a first generation total synthesis of vindoline that was extended to a series of related analogues,[14] we began examining protocols for their incorporation into vinblastine and its analogues. In these studies, we found that a single step biomimetic coupling of catharanthine with vindoline provides **1** directly in yields competitive with the best of the past protocols and that extends our 11-step synthesis of (−)-vindoline[14] to a 12-step total synthesis of vinblastine. Using improved conditions for a coupling first disclosed and developed by Kutney,[15] treatment of a mixture of catharanthine and vindoline with $FeCl_3$ (5 equiv, 23 °C), presumably generating the catharanthine amine radical cation which undergoes a subsequent oxidative fragmentation, leads to coupling providing the iminium ion **5** exclusively possessing the natural C16′ stereochemistry (Scheme 3). Reduction with $NaBH_4$ produces anhydrovinblastine (**4**) in superb conversion (90%), provided that CF_3CH_2OH, which solubilizes the reactants,[16] is used as a cosolvent with the aqueous 0.1 N HCl reaction solution.[17a] Moreover, *without reductive workup* and following a modified oxidation procedure of Sakamoto,[18] the reaction mixture containing the iminium ion **5** can be added to a second Fe(III) solution ($Fe_2(ox)_3$) cooled to 0 °C and saturated with air. Subsequent addition of $NaBH_4$ initiates both reduction of the intermediate iminium ion[17b] 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 (21%), along with anhydrovinblastine (**4**, 10%). The yield of coupled material exceeds 75% with the combined yield of C20′ alcohols being 62% (2:1 β:α oxidation). This one-step coupling reaction was conducted to

Scheme 1

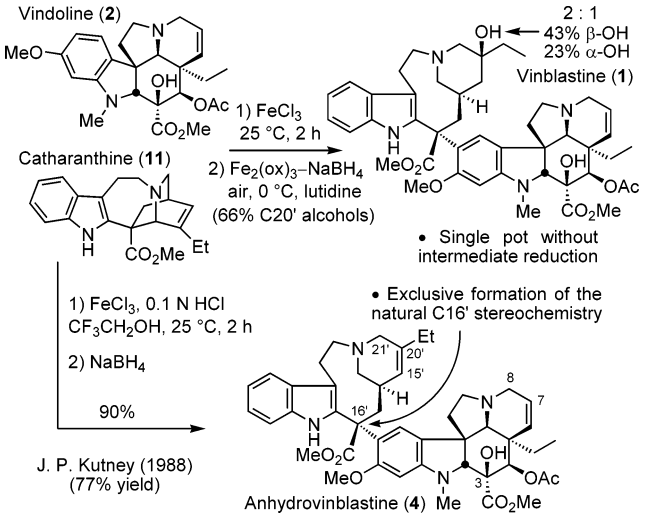


10.1021/ja078192m CCC: $40.75

Scheme 2



Scheme 3



provide natural (+)-vinblastine as well as with synthetic *ent*-(+)-vindoline[14] and *ent*-(−)-catharanthine to provide *ent*-(−)-vinblastine ($[\alpha]^{23}_D$ −38 (*c* 0.05, $CHCl_3$)). Small improvements in the yield (lutidine: 43% **1**; DBU: 44% **1**) or diastereoselectivity (2,2′-bipyridine: 3:1) have been observed when the oxidation is run in the presence of an organic base, suggesting further optimization may be possible.

Although it is conceivable that the C20′ oxidation arises from 1,4-reduction of iminium ion **5** followed by enamine **6** oxidation, the oxidation of anhydrovinblastine (**4**) to **1** (50%) and its C20′ isomer leurosidine (15−20%) under the Fe(III)−$NaBH_4$/O_2 conditions without the intermediacy of **5**[17c] indicates this is not necessary to achieve C20′ hydroxylation. Thus, labeling studies ($NaBD_4$)[17] not only rule out the intermediacy of iminium ion **5** in the conversion of anhydrovinblastine (**4**) to vinblastine but they also rule out an Fe-catalyzed isomerization of **4** to enamine **6** and its resulting oxidation (no C21′ D incorporation).[17c] Additionally, studies that should promote a 1,4-reduction of iminium ion **5** (e.g., $NaCNBH_3$)[7] result in subsequent enamine **6** protonation and reduction, not C20′ oxidation. Finally, reactions run in D_2O led to no deuterium incorporation, $^{18}O_2$ labeling studies indicate the C20′ alcohol oxygen originates with O_2 and not solvent water, reactions run in the absence of O_2 led to selective reduction of the $\Delta^{15',20'}$-double bond providing C20′ deoxyvinblastine and its C20′ diastereomer (1:1.5, 67%),[17c] and the final oxidation reaction may be conducted on trisubstituted alkenes (e.g., β-citronellol) that lack an allylic tertiary amine.

Continued studies on the reaction including efforts to improve the C20′ hydroxylation diastereoselectivity are in progress as are its extension to the total synthesis of vinblastine analogues.

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

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(16) This cosolvent effect is not large for the vindoline/catharanthine coupling but is key to its extension to analogue synthesis which will be disclosed in due course.
(17) (a) $NaBD_4$ labeling in the preparation of anhydrovinblastine indicates one D incorporation at α-C21′. (b) $NaBD_4$ labeling for the production of vinblastine from **2** and **11** indicates D incorporation (two D) at α-C15′ and α-C21′. (c) Oxidation of anhydrovinblastine with Fe(III)−$NaBD_4$/O_2 leads to a single α-C15′ D incorporation. In the absence of O_2, the reduction leads to two D incorporations at α-C15′ and C20′.
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