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Iron(III)/$NaBH_4$-Mediated Additions to Unactivated Alkenes: Synthesis of Novel 20′-Vinblastine Analogues

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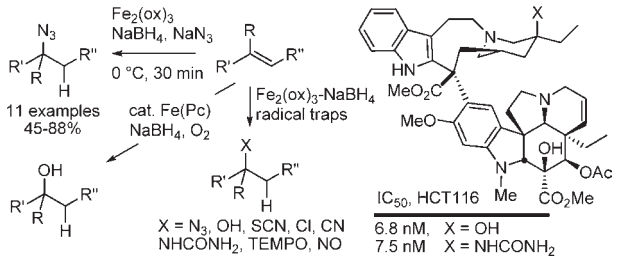
ABSTRACT



An Fe(III)/$NaBH_4$-mediated reaction for the functionalization of unactivated alkenes is described defining the alkene substrate scope, establishing the exclusive Markovnikov addition, exploring a range of free radical traps, examining the Fe(III) salt and initiating hydride source, introducing H_2O−cosolvent mixtures, and exploring catalytic variants. Its use led to the preparation of a novel, potent, and previously inaccessible C20′-vinblastine analogue.

Vinblastine and vincristine are the most widely recognized members of the vinca alkaloids and represent one of the earliest and most important contributions that plant-derived natural products have made to cancer chemotherapy.[1] Originally isolated from the leaves of *Catharanthus roseus* (L) G. Don[2] in trace quantities, their biological properties were among the first shown to inhibit the formation of microtubules and mitosis that is regarded today as one of the more successful drug targets for the treatment of cancer. Because of their clinical importance, structural complexity, and low natural abundance, they have been the subject of extensive and continuing investigations.[3]

Previously, we reported a concise total synthesis of vinblastine, related natural products including vincristine, and key analogues that utilizes a one-pot, two-step, biomimetic Fe(III)-promoted coupling of catharanthine and vindoline and the subsequent in situ alkene oxidation to generate vinblastine directly.[4−6] Herein, we detail the results of initial investigations of the second stage of this process, the Fe(III)-mediated free radical oxidation of the anhydrovinblastine trisubstituted alkene to introduce the vinblastine C20′ tertiary alcohol, providing a simple method for direct functionalization of unactivated alkenes. Included in these studies are a definition of the alkene substrate scope, the establishment of exclusive Markovnikov addition regioselectivity, the use of alternative radical traps, an examination of the Fe(III) salt and

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the hydride source required to initiate the reaction, and the introduction of alternative reaction solvents beyond the water and aqueous buffer[4] we originally disclosed. The extension of the results of these studies for the preparation of a key series of otherwise inaccessible vinblastine analogues bearing alternative C20′ functionalization is detailed.

The substrate scope and optimization of the reaction parameters were first examined with the hydroazidation of alkenes.[4,7] In part, we focused initially on the azide introduction not only because of their ability to serve as precursors to amines, but also because of their ability to serve as groups for photoaffinity or bioconjugation studies. Sodium azide (NaN_3) was found to be the most effective azide source for this reaction,[8] although LiN_3 and CsN_3 serve as attractive alternatives. Complementary to its use in water alone,[4] solvent mixtures of water (H_2O) with ethanol (EtOH), tetrahydrofuran (THF), or acetonitrile (MeCN) also provided good yields of the desired products. EtOH was an effective cosolvent for polar substrates with hydrogen bond donors, while THF was the optimal cosolvent when using nonpolar substrates. A survey of Fe(III) reagents revealed that ferric oxalate[9] [$Fe_2(ox)_3 > Fe_2(SO_4)_3 > FeCl_3 > Fe(NO_3)_3 > Fe(acac)_3$] performed best in the mixed solvent systems as it did in aqueous buffer.[4] $NaBH_4$ was the most convenient of the initiating hydride sources (vs $NaCNBH_3$, $LiBH_4$, $NaBH(OAc)_3$, BH_3) although $PhSiH_3$ also supports the reaction (> 24 h vs 30 min), whereas Bu_3SnH was ineffective. Unactivated terminal alkenes including styrenes, as well as di- and trisubstituted alkenes participate in the hydroazidation reaction effectively (Figure 1). The only substrate class examined that failed to participate is electron-deficient alkenes (e.g., **1l**) that undergo preferential conjugate reduction. A wide range of substrate functional groups are tolerated under the reaction conditions including unprotected alcohols, basic amines, phenols, free anilines, epoxides, carboxylic acids, and alkyl bromides, and proximal polar (**1d**) or halide (**1h**) groups did not result in cyclization or intramolecular atom transfer reactions. Finally, the hydroazidation reaction displayed the characteristic 5:1 axial selective delivery of the azide (**1e**) observed in radical reduction reactions.[10]

Alternative radical traps were found to be compatible with the reaction conditions. Potassium thiocyanate,[11] air (O_2),[4] and *N*-acetylsulfanilyl chloride[12] provided their respective addition product in good yields. Use of potassium cyanate, followed by workup with ammonium

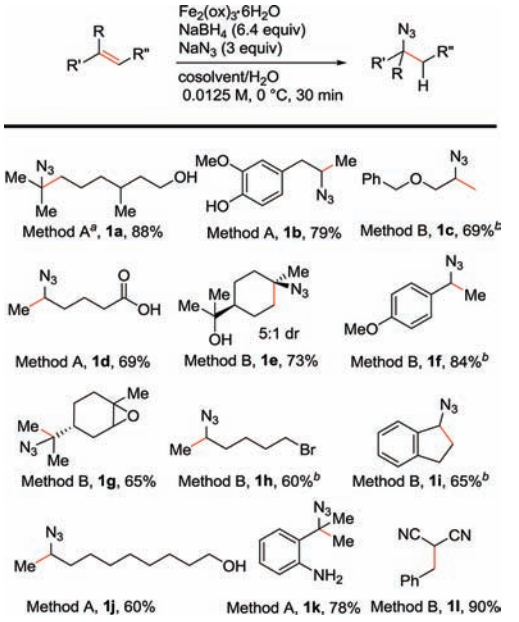

Figure 1. Alkene substrate scope. [a]Method A conditions: EtOH as cosolvent, $Fe_2(ox)_3 \cdot 6H_2O$ (2 equiv). Method B conditions: THF as cosolvent, $Fe_2(ox)_3 \cdot 6H_2O$ (3 equiv). [b]5 equiv of $Fe_2(ox)_3$ and 8 equiv of NaN_3 were employed.

hydroxide, provided the urea in 50% yield (Figure 2).[13] Tosyl cyanide[14] and TEMPO[4] provided their addition products in 35% and 44% yield, respectively. KSCN and KOCN have not been widely used as radical traps and may prove more generally useful. They display an interesting difference in radical trap regioselectivity with the thiocyanate trapping on sulfur, whereas addition to nitrogen is observed with cyanate. Although not exhaustively examined, this brief survey represents useful O, S, N, C, and halide functionalization of an alkene.

Although each of these alkene functionalizations is stoichiometric in its use of Fe(III), we found that the oxidation reaction using O_2 can be conducted in a catalytic fashion using phathalocyanine–Fe(II) (FePc) where O_2 serves as both the radical trap and metal oxidant. Thus, extending the oxidation of styrenes disclosed by Kasuga,[15] the FePc-catalyzed (5 mol %) reaction proved general in its substrate scope, oxidizing a range of alkenes to the corresponding alcohols (Figure 3).

Complementary to the mechanistic studies conducted on the oxidation of anhydrovinblastine to vinblastine,[4] the reaction of diethyl diallylmalonate was used to further probe the mechanism (Scheme 1). In the presence of NaN_3, the cyclized product **4** was observed in a 25% yield, along with byproduct **5** (32%).[16] No product arising from simple addition to the alkene was observed. Additionally, both

(7) For a Co-catalyzed hydroazidation of alkenes using sulfonyl azides and silanes, see: (a) Waser, J.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 8294. (b) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693.

(8) Arylsulfonyl azides were also found to be a competent azide source.

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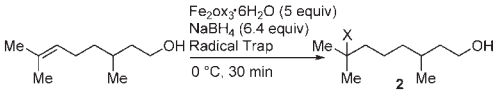


entry[a]	radical trap (equiv)	product	yield
1	NaN_3 (3)	X = N_3, **1a**	88%
2	KSCN (10)	X = SCN, **2a**	77%
3	air	X = OH, **2b**	68%[4]
4	4-AcNHC$_6$H$_4$SO$_2$Cl (5)	X = Cl, **2c**	62%
5	KOCN (10)	X = NHCONH$_2$, **2d**	50%
6	TsCN (4)	X = CN, **2e**	35%
7	TEMPO (3)	X = TEMPO, **2f**[b]	44%[4]
8	$NaNO_2$ (60)	X = NO, **2g**	41%[4]

Figure 2. Alternative radical traps. [a]See the Supporting Information for conditions. [b]44% **2f** + 44% **2b**.

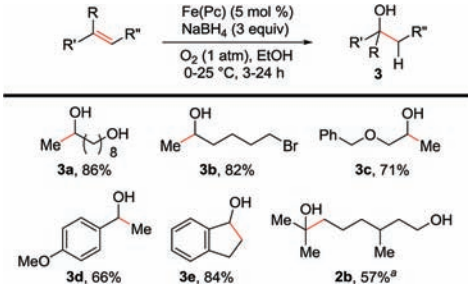
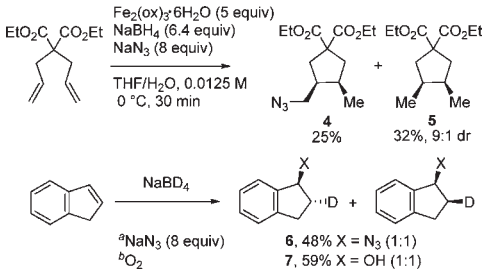


Figure 3. Fe(*Pc*) oxidation of unactivated alkenes. [a]2 equiv of $NaBH_4$ was employed.

the hydroazidation and oxidation of indene using $NaBD_4$ were found to be nondiastereospecific (Scheme 1). These results, combined with our prior mechanistic studies,[4] are consistent with an Fe/$NaBH_4$-mediated addition of a hydrogen atom to the alkene to form an alkyl free radical.[17,18]

Our interest in the Fe(III)−$NaBH_4$ mediated reactions stems from not only its use in accessing vinblastine but also the opportunity it presented for preparing otherwise inaccessible analogues incorporating modified C20′ functionality. Although this site is known to be critical to the properties of vinblastine[19] and is found deeply imbedded in

Scheme 1[a]



[a] $Fe_2(ox)_3 \cdot 6H_2O$ (5 equiv), THF-H_2O. [b] Fe(*Pc*) (5 mol %), EtOH.

the tubulin bound complex,[20] the examination of C20′ substituent effects has been limited. To date, semisynthetic modifications have been limited to *O*-acylation, the elimination of the 20′ alcohol, and subsequent alkene reduction or superacid-catalyzed additions.[21] These invariably led to substantial reductions in biological potency of the resulting derivative, albeit with examination of only a few key analogues.

With the benefit of continued studies beyond our initial survey,[4] several new C20′ derivatives have now been prepared and improvements introduced for many of those initially disclosed. Central to our continuing studies, the prior two-step biomimetic coupling of catharanthine and vindoline using NaN_3 as the radical trap provided exclusively 20′-azidoleurosidine (**10b**), bearing the undesired C20′ stereochemistry. Although this represented a superb conversion for both coupling and subsequent anhydrovinblastine hydroazidation (47%), it did not provide the C20′ diastereomer corresponding to vinblastine. The evaluation of alternative azide sources (Figure 4) revealed that CsN_3 provides 20′-azidovinblastine (**10a**) as a 1:3 mixture of diastereomers in an improved and superb combined 74% yield.

The yield of our previously reported 20′-TEMPO-vinblastine (**11a**) doubled from 18% to 36% by using cosolvent conditions, and the combined yield of biomimetic coupling and C20′ functionalization increased from 27% to 61%. The 20′-thiocyanoleurosidine diastereomer (**12b**) was the exclusive product when using KSCN as a radical trap, whereas addition of CsF or CeF_3 provided 20′-thiocyanovinblastine (**12a**) as a mixture of vinblastine/leurosidine diastereomers (1:2 and 1:3, respectively). Although not investigated in detail, the Mukaiyama Co(II)-catalyzed alkene oxidation ($Co(acac)_2$, O_2, $PhSiH_3$)[22] failed to convert anhydrovinblastine to vinblastine, and Carreira's Co-catalyzed alkene hydroazidation[7] did not provide **10a**/**10b**.

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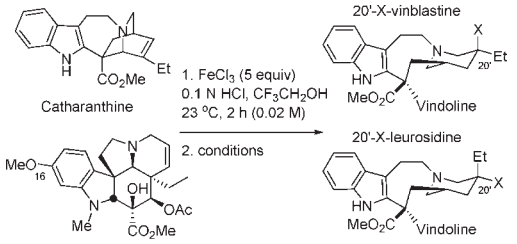
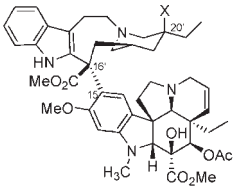


conditions	20'-X-vinblastine	20'-X-leurosidine
$Fe_2(ox)_3$ (10 equiv), $NaBH_4$ (20 equiv) air, 0 °C, H_2O	**8a**, 50%	**8b**, 20%
$Fe_2(ox)_3$ (10 equiv), $NaBH_4$ (20 equiv) no additive, 0 °C, H_2O	**9a**, 27%	**9b**, 40%
$Fe_2(ox)_3$ (10 equiv), $NaBH_4$ (20 equiv)		
LiN_3 (60 equiv), 0 °C, H_2O	-------	**10b**, 43%
NaN_3 (60 equiv), 0 °C, H_2O	-------	**10b**, 47%
CsN_3 (30 equiv), 0 °C, H_2O	**10a**, 20%	**10b**, 54%
$Fe_2(ox)_3$ (30 equiv), $NaBH_4$ (20 equiv)		
TEMPO (5 equiv), 0 °C, H_2O	**11a**, 18%	**11b**, 9%
TEMPO (5 equiv), 0 °C, H_2O/EtOH	**11a**, 36%	**11b**, 25%
$Fe_2(ox)_3$ (10 equiv), $NaBH_4$ (20 equiv) 0 °C, H_2O/EtOH		
KSCN (60 equiv)	-------	**12b**, 40%
KSCN (60 equiv)/CsF (60 equiv)	**12a**, 10%	**12b**, 16%
KSCN (240 equiv)/CeF_3 (60 equiv)	**12a**, 10%	**12b**, 32%

Figure 4. Additional vinblastine C20′ functionalization studies.



compound	IC_{50} (nM) L1210	HCT116	HCT116/VM46
X = OH, **8a**	6.0	6.8	600
X = H, **9a**	50	60	600
X = N_3, **10a**	670	690	5500
X = TEMPO, **11a**	4000	3800	5600
X = SCN, **12a**	560	550	2900
X = NH_2, **13a**	640	600	>10000
X = NHCHO, **14a**	65	85	6500
X = $NHCOCH_3$, **15a**	65	90	7500
X = $NHCOCF_3$, **16a**	660	690	8100
X = $NHCO_2CH_3$, **17a**	50	75	2600
X = $NHCONHCOCCl_3$, **18a**	45	6.0	1600
X = $NHCONH_2$, **19a**	40	7.5	4400
X = $NHCSNH_2$, **20a**	55	7.7	2000
X = NCS, **21a**	590	530	7000

Figure 5. Biological evaluation of 20′-vinblastine analogues.

The consequences of securing access to 20′-azidovinblastine (**10a**) were that it provided the opportunity to prepare and examine 20′-aminovinblastine (**13a**) and its derivatives. Reduction ($NaBH_4$–$CoCl_2 \cdot 6H_2O$,[23] THF–H_2O (1:1), 71%) of **10a** provided 20′-aminovinblastine (**13a**) in a good yield, and a key series of 20′-vinblastine analogues (**14a**–**21a**) were prepared by derivatization of **13a**. Similarly, the 20′-aminoleurosidine (**14b**–**19b**) derivatives were accessed from **10b** where the acylation of the sterically more accessible equatorial amine occurs at a faster rate (see the Supporting Information).

The 20′-vinblastine and 20′-leurosidine analogues were examined for cytotoxic activity against L1210, HCT116, and HCT116/VM46, the latter of which exhibits resistance to vinblastine through overexpression of Pgp. As expected, the 20′-vinblastine derivatives (Figure 5) proved more potent than the corresponding 20′-leurosidine analogues (10- to 100-fold, see the Supporting Information), with the exception of **10a** and **12a** which were essentially equipotent with their 20′-leurosidine analogues. The azide **10a** (X = N_3), thiocyanate **12a** (X = SCN), and thioisocyanate **21a** (X = NCS), as well as the 20′ free amine **13a** (X = NH_2) proved to be 100-fold less active than vinblastine (**8a**, X = OH) and 10-fold less active than 20′-deoxyvinblastine (**9a**, X = H). In contrast, the key series of amine derivatives prepared from **13a** exhibited progressively improved potency as one moves through the series of amide, carbamate, and urea derivatives such that the latter ureas **18a** and **19a** approach (L1210) or match (HCT116) the activity of vinblastine itself. The derivative **18a** rapidly hydrolyzes to the urea **19a** under the assay conditions, most likely accounting for their indistinguishable activity. The most distinguishing feature in this series is the progressively reduced acidity of the functionalized HN, and its progressively diminished H–bond donor capability ($HNCOCF_3$ > $HNCOCH_3$ = HNCHO > $HNCO_2Me$ > $HNCONH_2 \approx$ OH) culminating in the urea **19a**, which most closely matches such properties of a free alcohol.

An initial examination of an Fe(III)/$NaBH_4$-mediated reaction for the functionalization of unactivated alkenes is reported enlisting a range of free-radical traps. Its application in a one-pot, two-step biomimetic coupling of vindoline with catharanthine provided a key series of previously inaccessible 20′-vinblastine analogues, one of which matches the potency of vinblastine. These latter studies highlight the robust nature of the methodology, demonstrating its utility to selectively functionalize alkenes in an unprotected complex natural product.

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

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The authors declare no competing financial interest.