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Synthesis of C-15 Vindoline Analogues by Palladium-Catalyzed Cross-Coupling Reactions

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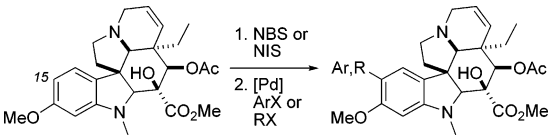

Described are general protocols for the rapid construction of various C-15-substituted analogues of vindoline using palladium-catalyzed cross-coupling reactions. The required bromo- and iodovindolines were prepared in high yield by the reaction of vindoline with *N*-bromosuccinimide or *N*-iodosuccinimide, respectively. The study not only led to the preparation of a number of structurally novel vindoline analogues but also opens the door to new strategies for the synthesis of vinblastine, vincristine, and related anticancer agents. Also described is the conversion of *ent*-tabersonine to *ent*-vindoline.

Vinblastine (**1**) and vincristine (**2**) are two bisindole alkaloid natural products isolated from the Madagascar periwinkle, *Catharanthus roseus* G. Don (Figure 1).[1] Both possess considerable antimitotic activity and thus have found use in treatment for various carcinomas, particularly childhood leukemia and Hodgkin's disease.[2] The low natural availability and cytotoxic properties of these molecules have meant that considerable synthetic efforts have been expended to find efficacious analogues. In the 40 years since the isolation of vinblastine, two such compounds, vindesine (**3**, Eldesine, Lilly)[3] and vinorelbine (**4**, Navelbine, Pierre-Fabre),[4] have found use in clinical treatment. A third, vinflunine (**5**, Javlor, Pierre-Fabre/Bristol-Myers-Squibb), is currently in phase III clinical trials.[5] The suggestion that these latter two compounds have similar, but different, modes of action to the natural compounds is encouraging for the prospect of further analogues to tackle cross-resistance.

In addition, there have been a number of efforts to synthesize vinblastine, both de novo and semisynthetically, from the much more naturally abundant vindoline and catharanthine by connection between C-15 at the former and C-18′ at the latter.[6] The coupling of these compounds has been accomplished several times and inevitably takes advantage of the nucleophilicity of vindoline at C-15.[7] Recent efforts by Fahy have also made use of this reactivity to elaborate the vindoline skeleton by addition to glycolates.[8] Our interest in the total synthesis of vinblastine drew our attention to the possibility of installing a halogen at C-15 of vindoline, which would allow for further elaboration at this position by utilizing the broad spectrum of cross-coupling reactions.[9] These reactions are typically performed under mild conditions and provide a high degree of functional group tolerance. The implementation of this chemistry would allow introduction of novel substituents at C-15, in addition to providing a versatile scaffold from which further synthetic elaborations could provide a new synthesis of vinblastine, vincristine, and related compounds.

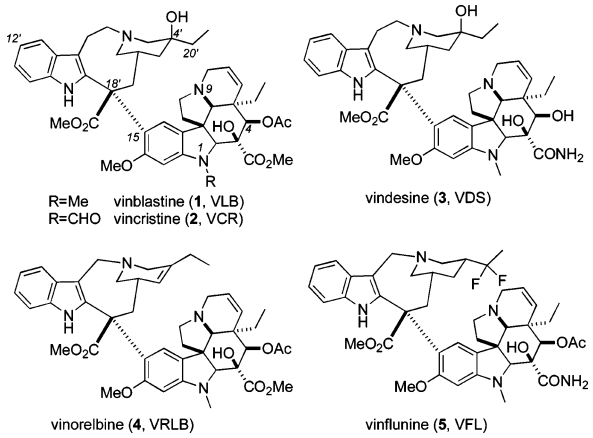

FIGURE 1. Clinically efficacious bisindole alkaloids and derivatives.

Initial concerns about the electron-rich nature of the aryl ring, which slows down oxidative addition of Pd, prompted us to first investigate the feasibility of cross-coupling of such systems using a model compound. Thus a substituted carbazole containing the essential features of 15-bromovindoline was first synthesized to

(1) (a) Noble, R. L.; Beer, C. T.; Cutts, J. H. *Ann. N.Y. Acad. Sci.* **1958**, *76*, 882. (b) Svoboda, G. H.; Neuss, N.; Gorman, M. *J. Am. Pharm. Assoc. Sci. Ed.* **1959**, *48*, 659.

(2) For a review of the medicinal chemistry of vinblastine, see: Antitumor Bisindole Alkaloids from *Catharanthus* roseus (L.). *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press, Inc.; San Diego, 1990; Vol. 37, Chapters 3 and 4, pp 133−204.

(3) (a) Barnett, C. J.; Cullinan, G. J.; Gerzon, K.; Hoying, R. C.; Jones, W. E.; Newlon, W. M.; Poore, G. A.; Robison, R. L.; Sweeney, M. J.; Todd, G. C.; Dyke, R. W.; Nelson, R. L. *J. Med. Chem.* **1978**, *21*, 88. (b) Gokbuget, N.; Hoelzer, D. *Leuk. Lymphoma* **1997**, *26*, 497.

(4) (a) Potier, P. *Semin. Oncol.* **1989**, *16*, 2. (b) Gregory, R. K.; Smith, I. E. *Br. J. Cancer* **2000**, *82*, 1907.

(5) (a) Fahy, J.; Duflos, A.; Ribet, J. P.; Jacquesy, J. C.; Berrier, C.; Jouannetaud, M. P.; Zunino, F. *J. Am. Chem. Soc.* **1997**, *119*, 8576. (b) Hill, B. T. *Curr. Pharm. Des.* **2001**, *7*, 1199.

(6) (a) For a review on synthetic studies, see: Antitumor Bisindole Alkaloids from *Catharanthus roseus* (L.). *The* Alkaloids; Brossi, A., Suffness, M., Eds.; Academic Press, Inc.; San Diego, 1990; Vol. 37, Chapter 2, pp 77−131. (b) Mangeney, P.; Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1979**, *101*, 2243. (c) Kutney, J. P.; Choi, L. S. L.; Nakano, J.; Tsukamoto, H.; McHugh, M.; Boulet, C. A. *Heterocycles* **1988**, *27*, 1845. (d) Kuehne, M. E.; Matson, P. A.; Bornmann, W. G. *J. Org. Chem.* **1991**, *56*, 513. (e) Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232. (f) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Ayato, S.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137.

(7) (a) Harley-Mason, J.; Atta-Ur-Rahman. *Tetrahedron* **1980**, *36*, 1057. (b) Kutney, J. P.; Beck, J.; Bylsma, F.; Cretney, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 4504. (c) Magnus, P.; Mendoza, J. S.; Stamford, A., Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232. (d) Langlois, N.; Gueritte, F.; Langlois, Y., Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017. (e) Vukovic, J.; Goodbody, A. E.; Kutney, J. P.; Misawa, M. *Tetrahedron* **1988**, *44*, 325. (f) Misawa, M.; Endo, T.; Goodbody, A.; Vukovic, J.; Chapple, C.; Choi, L.; Kutney, J. P. *Phytochemistry* **1988**, *27*, 1355. Tabakovic, T.; Gunic, E.; Juranic, I. *J. Org. Chem.* **1997**, *62*, 947.

(8) Fahy, J.; du Boullay, V. T.; Bigg, D. C. H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 505.

(9) During the preparation of this manuscript, a communication describing some similar transformations was published: Fekete, M.; Kalonits, P.; Novak, L. *Heterocycles* **2005**, *65*, 165. This communication reports the slow nature of the Suzuki coupling of 15-bromovindoline, in contrast to our findings.

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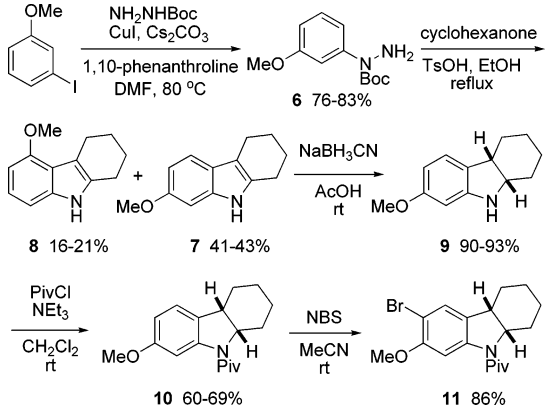
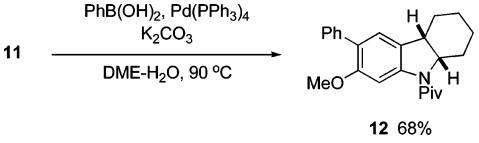
SCHEME 1. Synthesis of Model Compound 11



SCHEME 2. Suzuki Reaction of 11 with Phenylboronic Acid

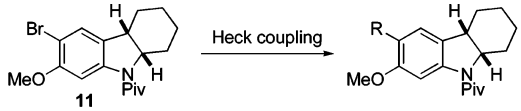


serve as a platform for the development of optimum protocols for the cross-coupling reactions.

A. Cross-Couplings of Model Compound. The required model compound (**11**) was synthesized by a five-step sequence as shown in Scheme 1. Boc-hydrazine **6**, a single regioisomer, was prepared in 76−83% yield following the known procedure.[10] Treatment of this hydrazine with tosic acid and cyclohexanone in refluxing ethanol promoted in situ removal of the carbamate followed by the Fischer-indole reaction.[11] Two regioisomeric indoles were formed, due to the substitution pattern of the hydrazine, and these were separated by column chromatography to give pure indoles **7**[12] and **8**[13] in 41−43% and 16−21% yields, respectively. Indole **7** was reduced using $NaBH_3CN$ in the presence of AcOH to give **9** as a single diastereomer, which was protected directly as the pivalate (**10**) in good yield. Early exploration of the bromination of this system had shown that attenuation of the reactivity of the nitrogen lone pair was necessary to provide highly selective halogenation para to the amine, without competing dihalogenation. The desired bromination was achieved by simple treatment of the aniline with NBS in MeCN at room temperature to afford **11** in 86% yield (Scheme 1).

Compound **11** was evaluated as a partner in various palladium-catalyzed cross-coupling processes. Among these, the Suzuki reaction is arguably the most robust, so it was investigated first. The Suzuki coupling of **11** and phenylboronic acid proceeded smoothly under standard conditions to give the expected biaryl (**12**) in 68% yield (Scheme 2). We next examined the Heck reaction of **11** with a number of coupling partners. Considerable effort was put into optimizing the conditions for this coupling, since it was expected to prove useful in other endeavors, such as the synthesis of vinblastine and analogues. Table 1 shows the various conditions employed in the Heck coupling of **11** and methyl acrylate. It is clear that although the Heck reactions worked well, the yields, even under optimized conditions, barely

TABLE 1. Heck Couplings of Aryl Bromide 11[a]



entry	coupling partner	solvent	product; R	yield(%)[b]
1	methyl acrylate	DMF NEt_3 (1:1)	MeO_2C **13**	57 (57)
2	methyl acrylate	DMF n-Bu_3N (1:1)	**13**	62 (67)
3	methyl acrylate	DMF $MeNCy_2$ (1:1)	**13**	n.d.[c]
4	methyl acrylate	DMF NEt_3 (1 equiv.)	**13**	8 (11)[d]
5	methyl acrylate	DMF n-Bu_3N (1 equiv.)	**13**	30 (49)[d]
6	methyl acrylate	DMF $MeNCy_2$ (1 equiv.)	**13**	43 (76)[d]
7	methyl acrylate	DMA NEt_3 (1:1)	**13**	70 (70)
8	methyl acrylate	DMSO NEt_3 (1:1)	**13**	0
9	methyl acrylate	dioxane NEt_3 (1:1)	**13**	37 (37)
10	methyl acrylate	DMF NEt_3 (1:1)	**13**	15 (48)[e]
11	methyl vinyl ketone	DMA NEt_3 (1:1)	O **14**	49 (96)
12	methyl cinnamate	DMA NEt_3 (1:1)	Ph MeO_2C **15**	29 (29)
13	dimethyl maleate	DMA NEt_3 (1:1)	CO_2Me MeO_2C **16**	69 (69)

[a] Reactions were conducted using 5 equiv of alkene and 25 mol % of $PdCl_2[P(o\text{-tol})_3]_2$ at 100 °C until the reaction was judged complete by TLC. [b] Isolated yield. Yields in parentheses are based on recovered starting material. [c] Product contaminated with amine. [d] Reaction time was 24 h. [e] $Pd(OAc)_2[P(o\text{-tol})_3]_2$ was used as catalyst.

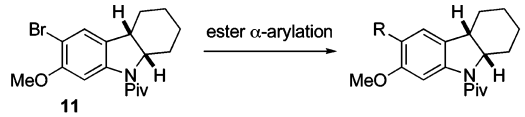
rivaled those of the Suzuki reaction. Best results were obtained using either *N*,*N*-dimethylformamide (DMF) or *N*,*N*-dimethylacetamide (DMA) as solvents and a large excess of a tertiary amine base. The yields were lower when the base was employed in stoichiometric amounts (entry 1 vs 4 and entry 2 vs 5). In most cases, the recovered starting material was contaminated with varying amounts of the corresponding dehalogenated compound. As reported in the literature,[14] the use of 1 equiv of $MeNCy_2$ as the base reduced the extent of dehalogenation, but at the price of a lower isolated yield (entry 6). Of the palladium catalysts examined, $PdCl_2[P(o\text{-tol})_3]_2$ gave the best results in terms of turnover and yield. The optimized Heck protocol also allowed the coupling of bromide **11** with methyl vinyl ketone (entry 11), methyl cinnamate (entry 12), and dimethyl maleate (entry 13).

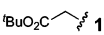
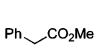
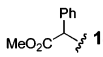
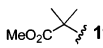
The coupling reactions of bromide **11** with ester enolates were also investigated.[15] Such reactions are of particular interest because of their direct applicability to the synthesis of vinblastine and analogues. Even from this brief study (Table 2) it is clear that a variety of enolates can participate in the arylation. Of particular interest is the result shown in entry 2, since it demonstrates the coupling with an arylacetic ester, as would be required for the synthesis of vinblastine.

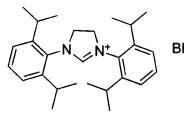
B. Cross-Coupling with Vindoline. Having confirmed the feasibility of various cross-coupling methods on model compound

(10) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.
(11) Lim, Y.-K.; Cho, C.-G. *Tetrahedron Lett.* **2004**, *45*, 1857.
(12) Banwell, M. G.; Kelly, B. D.; Kokas, O. J.; Lupton, D. W. *Org. Lett.* **2003**, 5, 2497.
(13) Kawase, M.; Miyake, Y.; Kikugawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1401.
(14) Gurtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107.
(15) (a) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402−3415. (b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234 and references therein. (c) Rawal, V. H.; Iwama, T. Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, August 26−30, 2001. ORGN-606 (CAS: AN 2001:640969).

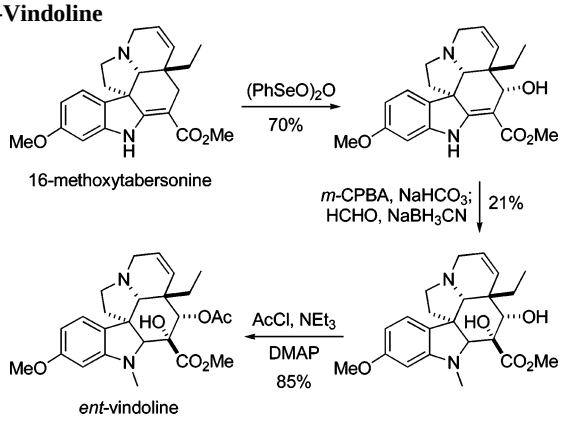
TABLE 2. Ester α-Arylations Using Bromide 11



entry	coupling partner	conditions	product; R	yield(%)
1		$Pd_2(dba)_3$, LiHMDS L*, $PhCH_3$, rt, 24 h	 **17**	54
2		$Pd_2(dba)_3$, LiHMDS L*, $PhCH_3$, 50 °C, 18 h	 **18**[a]	47
3		$Pd_2(dba)_3$, P^tBu_3, ZnF_2 DMF, 80 °C, 24 h	 **19**	59

L*: 

SCHEME 3. Conversion of *ent*-16-Methoxytabersonine to *ent*-Vindoline



11, we turned our attention to the cross-coupling reactions of vindoline. In previous studies from this laboratory, we had described the gram-scale enantioselective synthesis of tabersonine and 16-methoxytabersonine.[16] For the initial coupling studies, we converted synthetic *16-methoxy*tabersonine, which had been prepared in the enantiomeric form, to *ent*-vindoline through a sequence of three synthetic operations, following known procedures (Scheme 3).[17] Since the synthetic vindoline was precious and in the unnatural series, it was decided that all further transformations be carried out on natural vindoline. The conversion of vindoline to 15-bromovindoline (**20**) proved uneventful, since the conditions for bromination of the model system translated directly, allowing the formation of **20** in nearly quantitative yield (Scheme 4). The corresponding 15-iodovindoline (**33**, vide infra) was prepared similarly, in 97% yield, using NIS in MeCN.

B1. Suzuki Couplings. The conditions identified as effective for the Suzuki coupling of model compound **11** were utilized for the corresponding cross-couplings of bromovindoline with a broad range of boronic acids (Table 3). Arylboronic acids, irrespective of their electronic nature, afforded biaryl products (**21**−**26**) in good yields. Particularly encouraging is the ability to use hetero-

SCHEME 4. Bromination of Vindoline with NBS

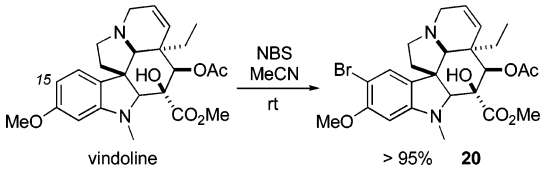
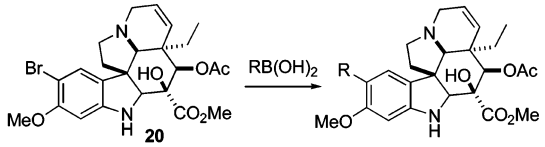
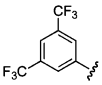
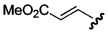
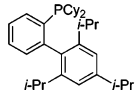


TABLE 3. Suzuki Couplings of Bromovindoline 20



entry	conditions[a]	product; R	yield(%)
1	$Pd(PPh_3)_4$, K_2CO_3 DME-H_2O, 1 h	 **21**	75
2	$Pd(PPh_3)_4$, K_2CO_3 DME-H_2O, 2 h	 **22**	59
3	$Pd(PPh_3)_4$, K_2CO_3 DME-H_2O, 14 h	 **23**	77
4	$Pd(PPh_3)_4$, K_2CO_3 DME-H_2O, 20 h	 **24**	38
5	$Pd(PPh_3)_4$, K_2CO_3 DME-H_2O, 23 h	 **25**	35
6	$Pd(PPh_3)_4$, K_2CO_3 DME-H_2O, 19 h	 **26**	45
7	$Pd(PPh_3)_4$, K_2CO_3 DME-H_2O, 18 h		49
8	$Pd(OAc)_2$, K_2CO_3, DPEphos $PhCH_3$, 16 h	**27**	0
9	$Pd(OAc)_2$, K_2CO_3, $PhCH_3$, 16 h 2-di-*tert*-butylphosphino biphenyl		10
10	$Pd(OAc)_2$, K_2CO_3, X-PHOS $PhCH_3$, 16 h		75
11	$Pd(PPh_3)_4$, K_2CO_3 DME-H_2O, 16 h	 **28**	30
12	$Pd(OAc)_2$, K_2CO_3, X-PHOS $PhCH_3$, 18 h		67
13	$Pd(OAc)_2$, K_2CO_3, X-PHOS $PhCH_3$, 18 h	 **29**	52
14[b]	$Pd(dppf)Cl_2$, KOAc, DMF, 16 h	 **30**	64

X-PHOS = 

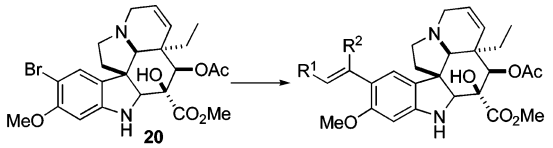
[a] All reactions were run at 90 °C, with 2 equiv of boronic acid. [b] Iodovindoline **33** was used.

arylboronic acids, which allow access to a broad range of arylated vindoline analogues. The strategic introduction of functionality on these partners, which mimic the "upper" portion of vinblastine, may allow the identification of new bioactive analogues of this important drug. Whereas arylboronic acids reacted smoothly under the original conditions, vinylboronic acids were less effective coupling partners, giving the products in moderate to low yields (entries 7 and 11). A ligand screen revealed that the commercially available X-PHOS ligand was highly effective at promoting this coupling.[18] The use of X-PHOS not only allowed couplings with vinylboronic acids (entries 10, 12) but also an alkylboronic acid (entry 13). Thus, compounds **27** and

(16) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628.

(17) (a) Barton, D. H. R.; Hui, R. A. H. F.; Ley, S. V.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1919. (b) Danieli, B.; Lesma, G.; Palmisano, G.; Riva, R. *J. Chem. Soc., Chem. Commun.* **1984**, 909. (c) Kobayashi, S.; Ueda, T.; Fukuyama, T. *Synlett* **2000**, 883.

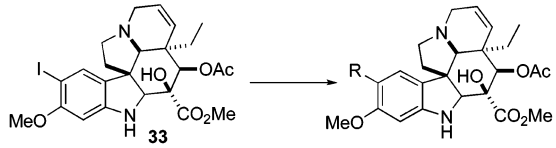
TABLE 4. Heck Couplings of Bromovindoline 20[a]



entry	coupling partner	solvent	product			yield(%)[b]
			R^1	R^2		
1	methyl acrylate	DMA-NEt_3 (1:1)	CO_2Me	H	**28**	29 (34)
2	methyl acrylate	DMF-NEt_3 (1:1)	CO_2Me	H	**28**	57 (57)
3	methyl acrylate	DMF-$MeNCy_2$ (1 eq.)	CO_2Me	H	**28**	45 (75)
4	styrene	DMF-$MeNCy_2$ (1 eq.)	Ph	H	**27**	50 (66)
5	methyl cinnamate	DMF-NEt_3 (1:1)	CO_2Me	Ph	**31**	42 (n.d.)[c,d]
6	dimethyl maleate	DMF-NEt_3 (1:1)	CO_2Me	CO_2Me	**32**	32 (n.d.)[c]

[a] Reactions were conducted using 5 equiv of alkene and 25 mol % of $PdCl_2[P(o\text{-tol})_3]_2$ at 100 °C until reaction was judged complete by TLC. [b] Isolated yield. Yields in parentheses are based on recovered starting material. [c] Recovered starting material contaminated with vindoline. [d] Product was obtained as a 4:1 mixture of diastereomers.

TABLE 5. Additional Coupling Reactions of Iodovindoline 33



entry	coupling partner	conditions	product; R		yield(%)
1	phenyl acetylene	$Pd(PPh_3)_4$, CuI, NEt_3 MeCN, 18 h, 80 °C	Ph—≡—	**34**	18[a]
2	phenyl acetylene	$Pd(PPh_3)_4$, CuI, NEt_3 MeCN, 18 h, rt	Ph—≡—	**34**	67
3	CO MeOH	$Pd(OAc)_2$, NEt_3, CO MeOH, 36 h, 65 °C	CO_2Me	**35**	60

[a] Bromovindoline was used.

28 were formed in 75% and 67% yields, respectively, and compound **29** was obtained in 52% yield. Of particular interest is entry 14, which shows the conversion of bromovindoline to the corresponding pinacol boronate. Ready access to this boronate has implications on the use of Suzuki cross-couplings for the preparation of vindoline analogues. At the present time, the scarcity of commercially available boronic acids is perhaps the biggest limitation of the Suzuki reaction. With the availability of vindoline boronate, it should be possible to use the vast array of commercially available aryl and vinyl halides and prepare innumerable analogues of vindoline.

B2. Heck Couplings. Bromovindoline (**20**) is also an effective substrate for the Heck reaction. The reaction of bromide **20** with various alkenes gave the expected coupled products in moderate yields (Table 4). DMF was found to be more effective as solvent than DMA in light of not only the yield but also the easier removal of solvent from product. Similar yields were obtained with 15-iodovindoline **33**, prepared analogously to bromide **20**.

B3. Other Couplings. Although ester α-arylation reactions with model compound **11** gave the desired products in good yields for three different esters (Table 2), the analogous reaction with the bromovindoline **20** proved unsuccessful. It is likely that the reaction is complicated by the presence of the unprotected hydroxyl as well as the methyl ester at C-3 and the acetate at C-4. No starting material could be isolated from the reaction, nor were any other products identified.

Given the versatility of Pd-catalyzed cross-coupling reactions, the halovindolines could be further elaborated in many different ways. We have examined two such transformations, the Sonogashira and the carbonylation reactions. Initially, the Sonogashira coupling of phenylacetylene with bromovindoline **20** was attempted, but it gave the coupled product in low yield, even at elevated temperatures. This problem was easily circumvented with 15-iodovindoline **33**, which reacted smoothly at room temperature to give the disubstituted acetylene **34** in 67% yield (Table 5). Iodovindoline was also a superior substrate for the carbonylation reaction. The reaction was carried out in methanol under an atmosphere of carbon monoxide using a catalytic amount of $Pd(OAc)_2$ and afforded the C-15 methyl ester (**35**) in good yield. The introduction of a carbonyl group at this position provides a useful handle for further elaboration, and an extra degree of freedom in the design of analogues of vinblastine.

We have established a number of protocols for the introductions of both aryl and aliphatic substituents at C-15 of vindoline by palladium-catalyzed cross-coupling, without the need for protection of the functionalized vindoline nucleus. The compounds thus formed represent a number of structurally novel vindoline analogues. In addition, this method should allow the introduction of more elaborate substituents, particularly achiral aromatic structures, which mimic the "upper" portion of vinblastine and thus represent a new class of vinblastine analogues.

Experimental Section

General Coupling Procedures. Suzuki A. A test tube was charged with bromovindoline **20** or iodovindoline **33** (1 equiv), K_2CO_3 (1.5 equiv), the arylboronic acid (2 equiv), and a magnetic stir bar. DME and water (3:1, to 0.1 M in halovindoline) were added, followed by $Pd(PPh_3)_4$ (10 mol %). The test tube was sealed with a septum and the stirred solution was purged of oxygen by five vacuum−argon cycles. The mixture was heated to 90 °C until TLC (50% acetone−hexane) indicated the absence of starting material (typically 2−4 h). The mixture was cooled, diluted with EtOAc, filtered through Celite, and concentrated. The crude product was purified by column chromatography, eluting with 25% acetone−hexane. General Heck A, Heck B, and Suzuki B coupling procedures and experimental details are in the Supporting Information. By the Suzuki A procedure, bromovindoline **20** (20 mg, 0.04 mmol) and phenylboronic acid gave the biaryl **21** (14.9 mg, 75%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (br s, 1H), 7.41 (m, 2H), 7.36 (m, 2H), 7.26 (m, 1H), 6.94 (s, 1H), 6.17 (s, 1H), 5.86 (ddd, J = 10.0, 5.0, 1.5 Hz, 1H), 5.49 (s, 1H), 5.25 (d, J = 10.0 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.78 (s, 1H), 3.50 (ddd, J = 16.0, 5.0, 1.0 Hz, 1H), 3.43 (m, 1H), 2.82 (br d, J = 16.0 Hz, 1H), 2.74 (s, 3H), 2.72 (s, 1H), 2.54−2.48 (m, 1H), 2.37−2.34 (m, 2H), 2.08 (s, 3H), 1.65 (dq, J = 15.0, 7.5 Hz, 1H), 1.20 (dq, J = 14.5, 7.5 Hz, 1H), 0.56 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 171.2, 158.2, 153.3, 139.3, 130.7, 129.7, 128.3, 126.6, 124.7, 124.5, 122.2, 94.0, 83.9, 79.9, 76.7, 67.3, 56.0, 53.3, 52.6, 52.3, 51.4, 44.3, 43.2, 38.9, 31.2, 21.4, 8.1; mp 107−112 °C; IR(film) 1742, 1245, 1039; MS calcd for $C_{31}H_{37}N_2O_6$ (MH^+) 533.2, found 533.1.

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Supporting Information Available: Detailed experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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