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TOTAL SYNTHESIS OF (–)- AND *ent*-(+)-4-DESACETOXY-5-DESETHYLVINDOLINE †

Hayato Ishikawa and Dale L. Boger*

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California, 92037

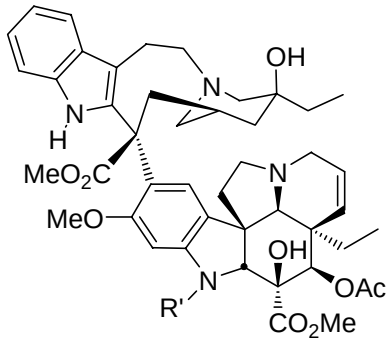
Abstract – A concise synthesis of (–)- and *ent*-(+)-4-desacetoxy-5-desethylvindoline (**2**), a key analogue of vindoline, is disclosed enlisting an intramolecular tandem [4+2]/[3+2] cycloaddition cascade of 1,3,4-oxadiazole (**5**) to assemble the pentacyclic skeleton of **2** in a single step that forms three new rings, four C–C bonds, and sets all five key stereocenters. The subsequent efforts on the elaboration of **6** to **2** revealed two subtle features key to our recent total syntheses of vindoline, vindorosine, and related natural products based on this strategy.

Vinblastine and vincristine constitute the most widely recognized members of the class of bisindole alkaloids as a result of their clinical use as antineoplastic drugs (Figure 1).[1] Originally isolated in trace quantities from *Cantharanthus roseus* (L.) G. Don,[2] 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 drug targets for the treatment of cancer.[3] Recently, we reported full details of the development of an usually concise total synthesis of (–)- and *ent*-(+)-vindoline (**1**), a major alkaloid of *Cantharanthus roseus* that constitutes the most complex half of vinblastine. It and related alkaloids were prepared by a route in which the pentacyclic skeleton complete with all substituents and stereocenters is created in a single step by a tandem intramolecular [4+2]/[3+2] cycloaddition cascade of a 1,3,4-oxadiazole that was inspired by the natural product structure.[4]

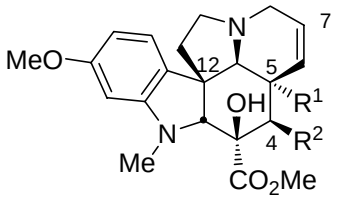
A key analogue of vindoline that we anticipate synthetically incorporating into a vinblastine analogue is 4-desacetoxy-5-desethylvindoline (**2**) which is lacking both the C4-acetoxy and C5-ethyl groups. The C4-acetoxy substituent, which lies at the external and solvent exposed face of the vinblastine-tubulin

† We would like to dedicate this work to Professor Y. Kishi, an inspirational scientist, on the occasion of his 70th birthday.

complex, can be removed from vinblastine without diminishing its in vitro potency or in vivo efficacy.[5] Unclear from the recently disclosed X-ray structure is the role of the vindoline C5-ethyl substituent.[6] Herein, we report the extension of our studies to the preparation of 4-desacetoxy-5-desethylvindoline (**2**) that not only will permit a direct assessment of the C5 substituent role, but that also revealed several key subtle features intrinsic to the synthetic route implemented for vindoline (**1**) itself.



R' = CH_3, Vinblastine
R' = CHO, Vincristine



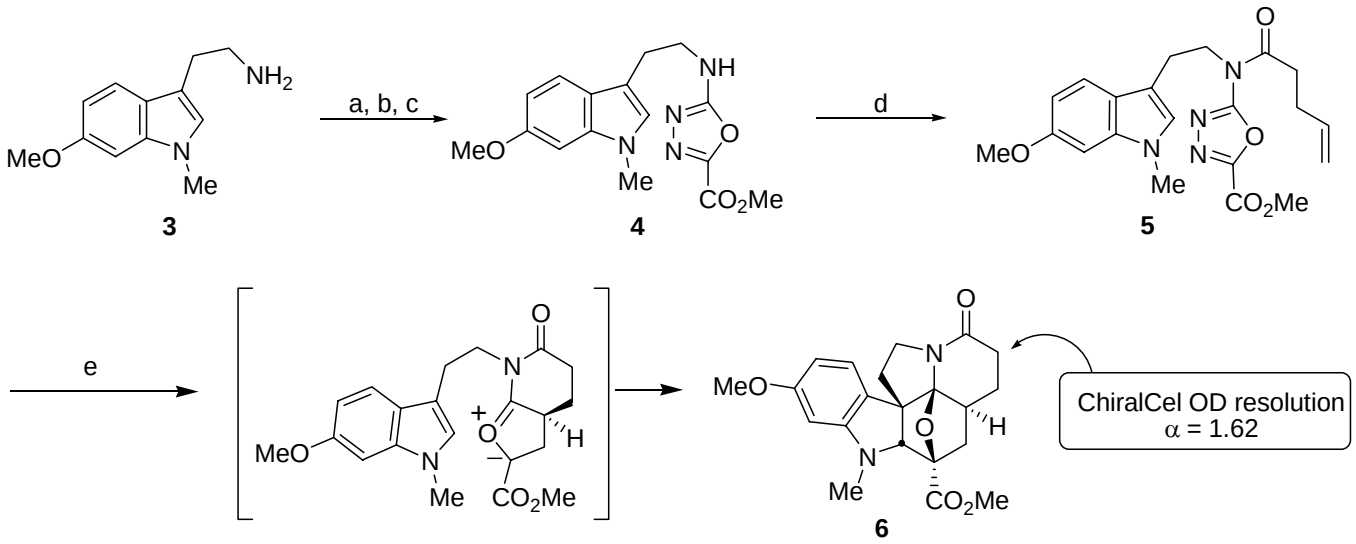
R^1 = Et, R^2 = OAc, Vindoline (**1**)
R^1 = H, R^2 = H, 4-Desacetyl-5-desethylvindoline (**2**)

Figure 1.

The synthesis of 4-desacetoxy-5-desethylvindoline (**2**) is based on an intramolecular variant of a 1,3,4-oxadiazole tandem [4+2]/[3+2] cycloaddition.[7] This reaction cascade is initiated by an intramolecular inverse electron demand Diels–Alder reaction of a dienophile tethered to the 1,3,4-oxadiazole and is followed by the loss of N_2 and a subsequent intramolecular 1,3-dipolar cycloaddition of a tethered indole that proceeds with exclusive endo diastereoselectivity directed to the face of the 1,3-dipole opposite the newly formed fused lactam. This cycloaddition cascade not only produces the pentacyclic skeleton of **2** and introduces all the requisite substituents and functionality, but it also sets all five stereocenters found in **2** in a single step. As such, the 1,3,4-oxadiazole cycloaddition cascade is ideally suited for the preparation of this class of natural products and their analogues.

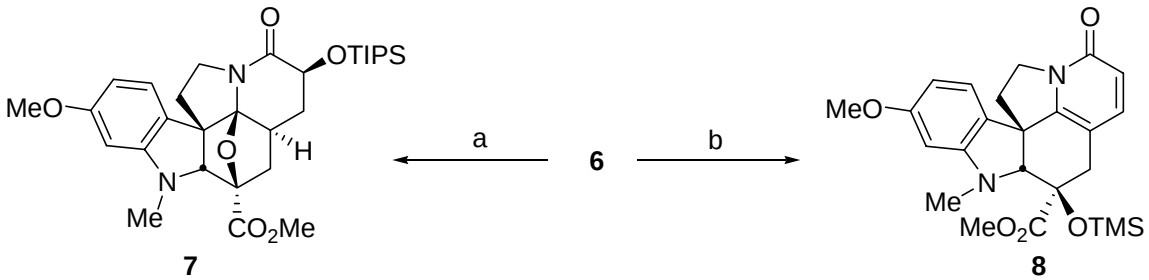
The requisite 1,3,4-oxadiazole (**4**) was prepared in three steps (Scheme 1) from *N*-methyl-6-methoxytryptamine (**3**) as previously disclosed.[4a] Thus, after treatment of **3** with 1,1-carbonyldiimidazole (CDI), the resulting imidazole urea (90%) was combined with methyl oxalylhydrazide[8] to give the corresponding semicarbazide (79%) which was dehydrated to **4** (81%) by treatment with *p*-toluenesulfonyl chloride and triethylamine in CH_2Cl_2. Oxadiazole (**4**) was coupled with 4-pentenoic acid providing the cycloaddition precursor (**5**) (97%). The tandem intramolecular cycloaddition reaction proceeded in superb yield (95%) upon warming a solution of **5** at 180 °C in *o*-dichlorobenzene for 15 h to provide **6** as a single diastereomer possessing the *Aspidosperma* alkaloid pentacyclic skeleton (natural enantiomer depicted). Cycloadduct (**6**) was readily resolved on a semipreparative ChiralCel OD column (2 × 25 cm, 15% EtOH–hexanes, 10 mL/min, t_R (natural) = 18.3 min and t_R (unnatural) = 29.7

min, α = 1.62). The absolute configuration of **6** was established by X-ray analysis of **15**, a heavy atom derivative prepared at a later stage.



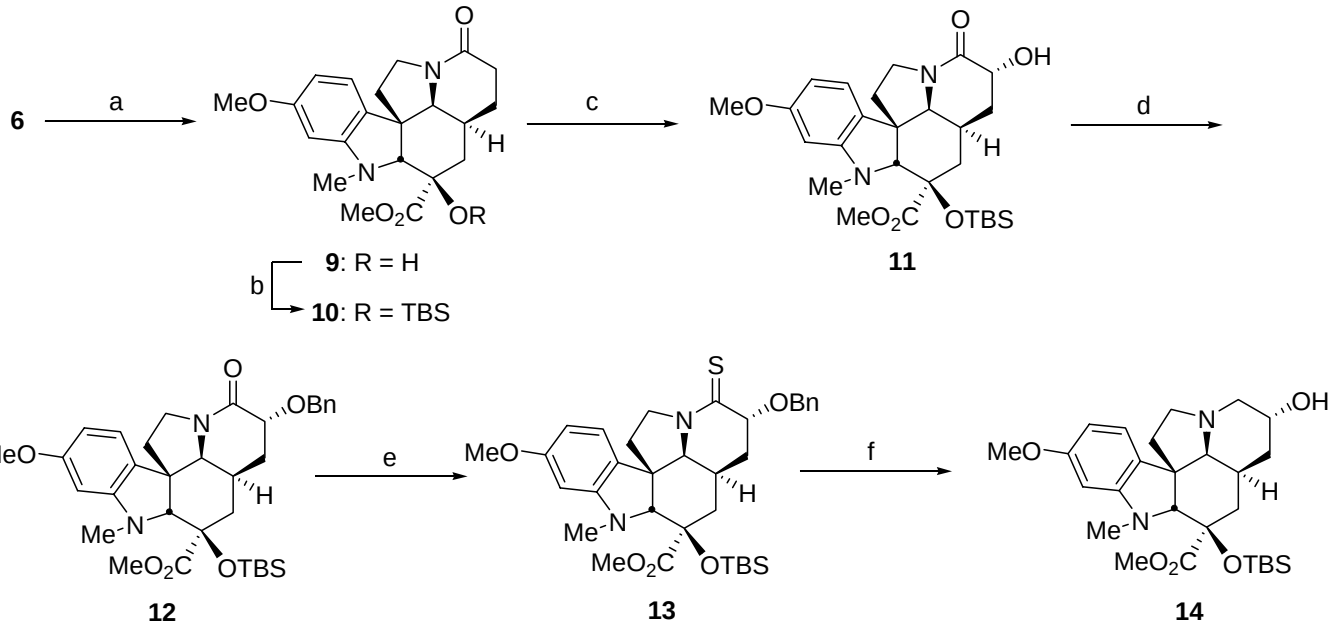
Scheme 1. Reagents and conditions: (a) CDI, THF, CH_2Cl_2, 23 °C, 90%. (b) methyl oxalylhydrazide, AcOH, THF, 40 °C, 79%. (c) TsCl, Et_3N, CH_2Cl_2, 23 °C, 81%. (d) 4-pentenoic acid, EDCI, DMAP, CH_2Cl_2, 23 °C, 97%. (e) 1,2-dichlorobenzene, 180 °C, 95%.

The first aspect of our vindoline synthesis that did not readily translate to **2** was the subsequent α-hydroxylation. Enlisting conditions developed for vindoline, α-hydroxylation of **6** with TMSO–OTMS and NaHMDS, followed by silyl ether protection of the isolated alcohol provided multiple components from which **7** could be isolated in only 20–30%, a yield that is much lower than any comparable substrate incorporating a C5-ethyl substituent (50–70%; 2 steps). Moreover, when **6** was treated with TMSOTf and *i*-Pr_2NEt at 23 °C for 30 min, the unusual pyridone (**8**) was isolated in excellent yield. This result illustrates that the oxido bridge of **6** is easily opened and, that in the absence of a C5-substituent and adjacent quaternary center, the intermediate iminium ion converts to an enamide (loss of H^+) which is further easily oxidized (Scheme 2).



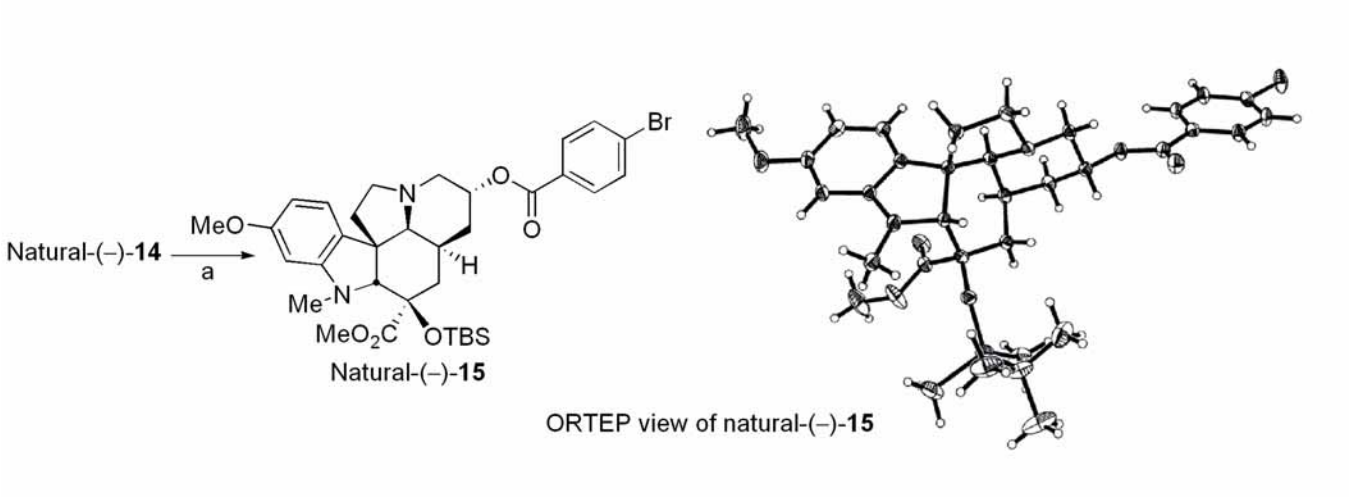
Scheme 2. Reagents and conditions: (a) 1) TMS_2O_2, NaHMDS, THF, –45 °C, 2) TIPSOTf, Et_3N, CH_2Cl_2, 23 °C, 20–30% (2 steps). (b) TMSOTf, *i*-Pr_2NEt, CH_2Cl_2, 23 °C, 87%.

To address this unexpected challenge, we elected to first reductively cleave the oxido bridge prior to α-hydroxylation. Thus, treatment of **6** with $NaCNBH_3$ in HCl–MeOH led to in situ acid-catalyzed oxido bridge cleavage and clean diastereoselective reduction of the intermediate acyl iminium ion to provide **9** in superb conversion (99%) (Scheme 3). Subsequent treatment of **9** with TBSOTf provided **10** (98%). α-Hydroxylation of **10** (6 equiv of TMSO–OTMS, 3 equiv of NaHMDS, –45 °C, 0.5 h) provided **11** possessing a C7 equatorial alcohol in a noticeably improved yield (79%). The stereochemistry resulting from the α-hydroxylation reaction, which now occurs from the less hindered α-face, was clear upon ^{1}H NMR analysis of **11** (C7-H; dd, J = 11.1, 7.3 Hz) and unambiguously established with an X-ray of **15**.[9] Thus, conducting the reaction on a substrate bearing a C5 hydrogen substituent with the oxide bridge cleaved resulted in a reversal of the α-hydroxylation diastereoselectivity (compare **7**) and this had an unexpected consequence on the penultimate olefin introduction discussed below. Protection of C7 alcohol of **11** was carried out with BnBr and catalytic *n*-Bu_4NI (87%) and was followed by thioamide formation with Lawesson's reagent[10] to provide **13** (99%). Reductive desulfurization with Raney-Ni conducted under conditions that also served to cleave the benzyl ether provided **14** (95%).



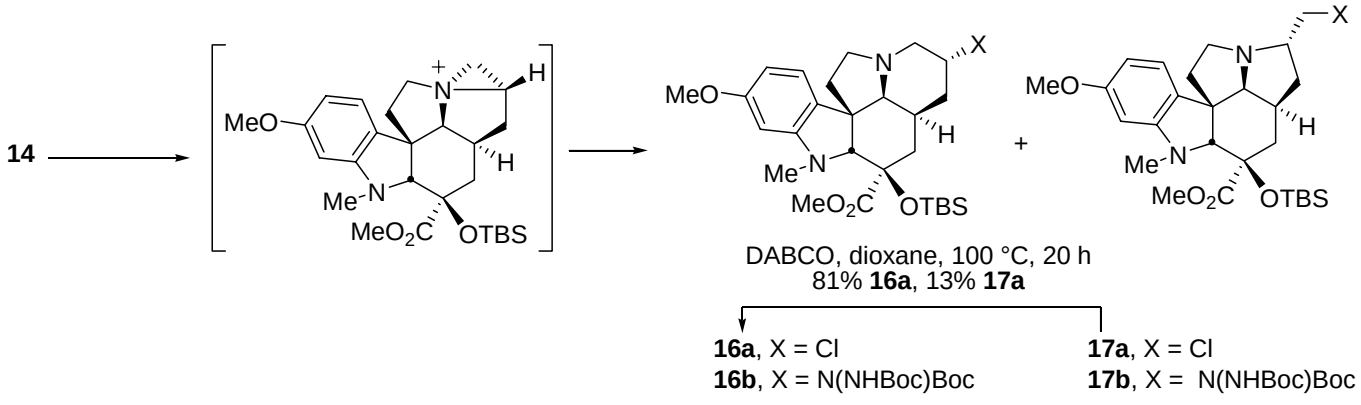
Scheme 3. Reagents and conditions: (a) AcCl, $NaCNBH_3$, MeOH, 23 °C, 99%. (b) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, 23 °C, 98%. (c) TMS_2O_2, NaHMDS, THF, –45 °C, 79%. (d) BnBr, NaH, *n*-Bu_4NI, THF, 23 °C, 87%. (e) Lawesson's reagent, toluene, 80 °C, 99%. (f) Ra-Ni, H_2, THF, 23 °C, 95%.

The relative stereochemistry and absolute configuration of **14** were established by X-ray analysis of **15** ($[\alpha]_D^{23}$ –17 (*c* 1.16, $CHCl_3$), recrystallized from EtOAc, mp 175–178 °C), a heavy atom derivative prepared by treatment of (–)-**14** ($[\alpha]_D^{23}$ –74 (*c* 1.17, $CHCl_3$) with 4-bromobenzoyl chloride (Scheme 4).[9]



Scheme 4. Reagents and conditions: (a) 4-bromobenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, 23 °C, 99%.

The second distinct of series of observations came upon attempted elimination of the equatorial C7 alcohol in **14** (Scheme 5, Table 1). Here, clearly the reaction proceeds via an intermediate aziridinium cation generated upon activation of C7 alcohol for elimination. Thus, initial efforts to promote the C7 alcohol elimination with Ph_3P–CCl_4 enlisting procedures first detailed by Kuehne[11] and later adopted by Fukuyama[12] failed to provide the olefin and afforded a mixture of **16a** and **17a**. When the reaction was conducted at low temperature, the ring contraction chloride (**17a**) proved to be major product (kinetic product), whereas reactions conducted at higher temperatures provided the direct chloride displacement product (**16a**) as the major product (≤10:1, thermodynamic product). In addition, the kinetic product (**17a**) smoothly transformed to the thermodynamic product (**16a**) when warmed at 100 °C (dioxane) even when conducted in the presence of base (DABCO) without evidence of productive elimination. Similarly, effort to promote the elimination reaction upon activation of the equatorial C7 alcohol with a Mitsunobu reagent[13] (Ph_3P–DTBAD) failed to provide the olefin and instead provided mixtures of **16b** and **17b**.



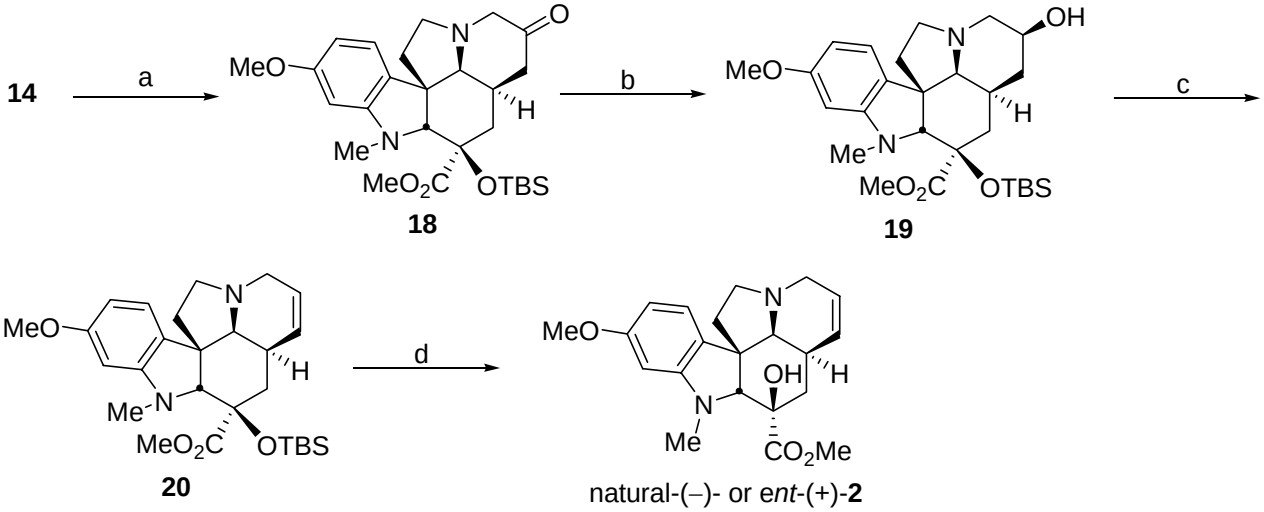
Scheme 5.

Table 1. Conditions Examined for Elimination of **14**

Conditions	Result[a]	
Ph_3P, CCl_4, Et_3N CH_3CN, 80 °C, 30 min	**16a** (91%)	**17a** (9%)
Ph_3P, CCl_4, CH_3CN, 80 °C, 30 min	**16a** (70%)	**17a** (30%)
Ph_3P, CCl_4, CH_3CN, 23 °C, 14 h	**16a** (41%)	**17a** (57%)
Ph_3P, CCl_4, CH_3CN, 0 °C,14 h	**16a** (30%)	**17a** (70%)
Ph_3P, DTBAD, THF, reflux, 24 h	**16b** (57%)	**17b** (43%)
Ph_3P, DTBAD, THF, 23 °C, 24 h	**16b** (50%)	**17b** (50%)

[a] Isolated yield

In marked contrast, when the C7 alcohol stereochemistry was inverted to provide the β-face axial alcohol analogous to the substrate enlisted for the preparation of vindoline,[4] the subsequent elimination reaction proceeds uneventfully (Scheme 6). Thus, oxidation of the C7 alcohol in **14** to provide **18** (Dess–Martin periodinane, 76%) in the presence of pyridine at 0 °C followed by L-selectride reduction (–78 °C, 96%) cleanly provided the isomeric axial alcohol (**19**). Treatment of **19** with Ph_3P–DEAD (THF) at room temperature resulted in regioselective elimination of the alcohol providing **20** (74%) and subsequent TBS ether deprotection (*n*-Bu_4NF, 97%) afforded **2**. [14]



Scheme 6. Reagents and conditions: (a) Dess–Martin periodinane, pyridine, CH_2Cl_2, 0 °C, 76%. (b) L-selectride, THF, –78 °C; $NaBO_3$, 96%. (c) DEAD, Ph_3P, THF, 23 °C, 74%. (d) *n*-Bu_4NF, THF, 23 °C, 97%.

Either the key regioselective elimination of **19** proceeds without the intermediacy of the corresponding aziridinium cation which is isomeric with that derived from **14**, or its fragmentation to the olefin is more facile and reagent nucleophilic attack on the sterically more encumbered centers less competitive. However, the detection of minor products derived from a $\Delta^{7,8}$ olefin (an enamine, vs $\Delta^{6,7}$ olefin) suggests the elimination reaction conducted on **19** proceeds without the intermediacy of an aziridinium cation.

In addition to providing both enantiomers of **2** that we anticipate utilizing to address the importance and role of the vinblastine C5 ethyl substituent, the studies revealed and clarified two subtle elements of our recently disclosed vindoline and vindorosine total syntheses.[4] The first is that the quaternary C5 center bearing the ethyl substituent along with the quaternary C12 center that flank the C19 center stabilize a labile oxido bridge in the cycloadducts by precluding elimination of a reversibly generated acyl iminium ion to the corresponding enamide or enamine. Secondly, and just an interestingly, the stereochemistry of the C7 alcohol is critical to conducting an effective and regioselective elimination to introduce the $\Delta^{6,7}$ olefin characteristic of vindoline and vindorosine.

Efforts on the incorporation of **2** into the corresponding vinblastine analogue are in progress as are the extension of these studies to preparation of additional vindoline analogues and they will be disclosed in due course.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. N. Norbert and M. N. Neuss, In *The Alkaloids*; ed. by A. Brossi and M. Suffness; Academic: San Diego, 1990; Vol. 37, pp. 229–240.
2. (a) R. L. Noble, C. T. Beer, and J. H. Cutts, *Ann. N. Y. Acad. Sci.*, 1958, **76**, 882. (b) R. L. Noble, *Lloydia*, 1964, **27**, 280. (c) G. H. Svoboda, N. Neuss, and M. Gorman, *J. Am. Pharm. Assoc. Sci. Ed.*, 1959, **48**, 659.
3. (a) R. J. Owellen, C. A. Hartke, R. M. Dickerson, and F. O. Hains, *Cancer Res.*, 1976, **36**, 1499. (b) H. L. Pearce, In *The Alkaloids*; ed. by A. Brossi and M. Suffness; Academic: San Diego, 1990; Vol. 37, 145.
4. (a) H. Ishikawa, G. I. Elliott, J. Velcicky, Y. Choi, and D. L. Boger, *J. Am. Chem. Soc.*, 2006, **128**, 10596. (b) Y. Choi, H. Ishikawa, J. Velcicky, G. I. Elliott, M. M. Miller, and D. L. Boger, *Org. Lett.*, 2005, **7**, 4539. (c) G. I. Elliott, J. Velcicky, H. Ishikawa, Y. Li, and D. L. Boger, *Angew. Chem. Int. Ed.*, 2006, **45**, 620. (d) Z.-Q. Yuan, H. Ishikawa, and D. L. Boger, *Org. Lett.*, 2005, **7**, 741.
5. (a) N. Neuss, A. J. Barnes, and L. L. Huckstep, *Experientia*, 1975, **31**, 18. (b) C. J. Barnett, G. J. Cullinan, K. Gerzon, R. C. Hoying, W. E. Jones, W. M. Nevlon, G. A. Poore, R. L. Robison, M. J.

Sweeney, G. C. Todd, R. W. Dyke, and R. L. Nelson, *J. Med. Chem.*, 1978, **21**, 88.

6. B. Gigant, C. Wang, R. B. G. Ravelli, F. Roussi, M. O. Steinmetz, P. A. Curmi, A. Sobel, and M. Knossow, *Nature*, 2005, **435**, 519.
7. (a) G. I. Elliott, J. R. Fuchs, B. S. J. Blagg, H. Ishikawa, H. Tao, Z.-Q. Yuan, and D. L. Boger, *J. Am. Chem. Soc.*, 2006, **128**, 10589. (b) G. D. Wilkie, G. I. Elliott, B. S. J. Blagg, S. E. Wolkenberg, D. R. Soenen, M. M. Miller, S. Pollack, and D. L. Boger, *J. Am. Chem. Soc*., 2002, **124**, 11292. (c) S. E. Wolkenberg and D. L. Boger, *J. Org. Chem*., 2002, **67**, 7361.
8. M. Christl, U. Lanzendoerfer, M. M. Groetsch, E. Ditterich, and J. Hegmann, *Chem. Ber.*, 1990, **123**, 2031.
9. The X-ray crystal structure of **15** (CCDC 609613) has been deposited with the Cambridge Crystallographic Data Centre.
10. S. O. Lawesson and B. S. Pedersen, *Tetrahedron*, 1979, **35**, 2433.
11. (a) M. E. Kuehne, F. J. Okuniewicz, C. L. Kirkemo, and J. C. Bohnert, *J. Org. Chem.*, 1982, **47**, 1335. (b) M. E. Kuehne and D. E. Podhorez, *J. Org. Chem.*, 1985, **50**, 924.
12. S. Kobayashi, T. Ueda, and T. Fukuyama, *Synlett*, 2000, 883.
13. (a) T. Iimori, Y. Ohtsuka, and T. Oishi, *Tetrahedron Lett.*, 1991, **32**, 1209. b) O. Mitsunobu, *Synthesis*, 1981, 1.
14. Data for **2**: ^{1}H NMR (500 MHz, C_6D_6) δ 6.67 (d, *J* = 8.0 Hz, 1H), 6.36 (dd, *J* = 2.2, 8.0 Hz, 1H), 6.20 (d, *J* = 2.2 Hz, 1H), 5.55–5.50 (m, 1H), 5.26–5.20 (m, 1H), 3.84 (d, *J* = 1.1 Hz, 1H), 3.43 (s, 3H), 3.56 (s, 3H), 3.00–2.80 (m, 2H), 2.65 (dd, *J* = 10.9, 14.5 Hz, 1H), 2.52 (s, 3H), 2.40–2.24 (m, 4H), 2.12–1.98 (m, 2H), 1.92 (q, *J* = 9.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 174.0, 161.6, 154.7, 131.9, 127.1, 123.0, 122.0, 104.0, 95.5, 80.3, 77.2, 68.0, 55.0, 53.8, 53.0, 52.3, 51.4, 42.3, 36.5, 32.2, 28.8; IR (film) ν_{max} 3452, 2929, 2805, 1738, 1615, 1500, 1463, 1435, 1358, 1338, 1244, 1225, 1170, 1092, 1070, 1032, 968, 948, 821, 790, 725 cm^{-1}; HRESI-TOF *m/z* 371.1976 ($C_{21}H_{26}N_2O_4$ + H^+ requires 371.1965). For natural **2**: $[\alpha]_D^{23}$ –12 (*c* 1.4, $CHCl_3$); for *ent*-**2**: $[\alpha]_D^{23}$ +12 (*c* 1.4, $CHCl_3$).