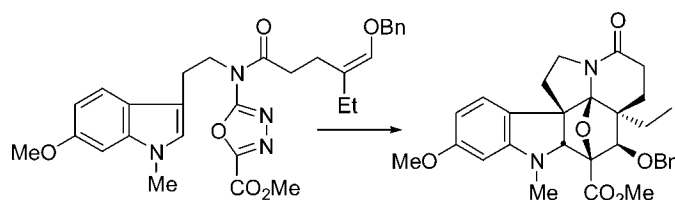


Total Synthesis of (–)- and
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Received August 15, 2005

ABSTRACT



Two exceptionally concise total syntheses of (–)- and ent-(+)-vindoline are detailed enlisting a diastereoselective tandem [4 + 2]/[3 + 2] cycloaddition of a 1,3,4-oxadiazole. The unique reaction cascade assembles the fully functionalized pentacyclic ring system of vindoline in a single step that forms four C–C bonds and three rings while introducing all requisite functionality and setting all six stereocenters within the central ring including three contiguous and four total quaternary centers.

Vinblastine (**1**) and vincristine (**2**) 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, which today is still regarded as one of the more successful drug targets for the treatment of cancer.³ In addition to being among the first natural products whose structures were determined by X-ray crystallography of a derivative, they were among the first for which X-ray was used to establish their absolute configuration.⁴ Vindoline (**3**),^{4,5} a major alkaloid of *Cantharanthus roseus*, constitutes the most complex half of vin-

blastine and serves as both a biosynthetic² and synthetic⁶ precursor to the natural product.⁷

Herein, we detail two first generation total syntheses of vindoline that complement past efforts,^{7–9} enlisting a unique tandem intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of 1,3,4-oxadiazoles.¹⁰ In these studies, key issues regarding the scope and stereochemical features of the cycloaddition cascade were defined and its potential for use in the construction of the vindoline structure was established. Thus, two concise routes to **3** are detailed enlisting the tandem

(1) Neuss, N.; Neuss, M. N. In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic: San Diego, 1990; Vol. 37, p 229.

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(4) Moncrief, J. W.; Lipscomb, W. N. *J. Am. Chem. Soc.* **1965**, 87, 4963.

(5) Gorman, M.; Neuss, N.; Biemann, K. *J. Am. Chem. Soc.* **1962**, 84, 1058.

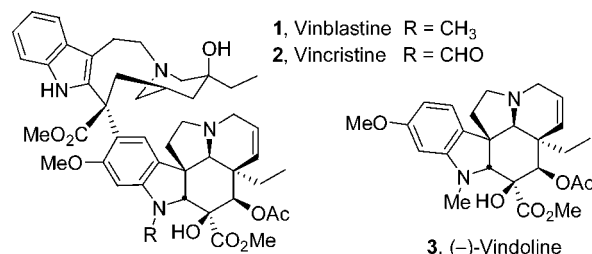


Figure 1. Natural product structures.

cycloaddition reactions of either 1,3,4-oxadiazole **4a** or **4b**, each of which assembles the fully functionalized pentacyclic ring system of **3** with formation of four C–C bonds and three rings in a single step, setting all six stereocenters within the central ring of vindoline including three contiguous and four total quaternary centers (Figure 2).

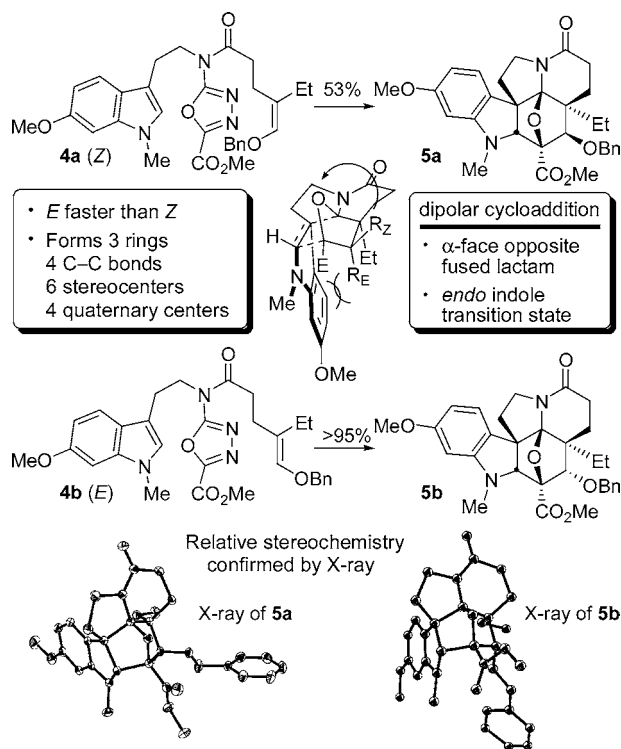


Figure 2. Key cycloaddition cascade.

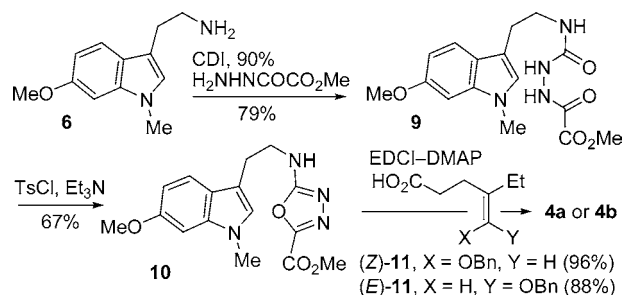
The preparation of the 1,3,4-oxadiazole precursors **4** is summarized in Scheme 1. Treatment of *N*-methyl-6-methoxytryptamine (**6**)¹¹ with phenyl carbonate followed by hydrazine provided **7** (64%), which was coupled with methyl oxalate (EDCI, DMAP, CH₂Cl₂, 23 °C, 61%) to provide **9** (see Supporting Information). Alternatively, **6** was first treated with carbonyldiimidazole (CDI) to form **8** (90%) and subsequently treated with methyl oxalylhydrazide¹² to furnish **9** (79%). Cyclization via dehydration of **9** (1.0 equiv of TsCl, 2.5 equiv of Et₃N, CH₂Cl₂, 67%) provided **10**, which was coupled with isomerically pure (*Z*)- or (*E*)-**11** to provide **4a** (96%) and **4b** (88%).

Both **4a** and **4b** undergo the tandem [4 + 2]/[3 + 2] cycloaddition cascade to give the pentacyclic products **5a**

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(7) Review: Kuehne, M. E.; Marko, I. In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic: San Diego, 1990; Vol. 37, p 77.

Scheme 1



and **5b**, respectively, as single diastereomers (Figure 2). The reaction leading to **5** is initiated by an intramolecular inverse electron demand Diels–Alder cycloaddition of the 1,3,4-oxadiazole with the tethered enol ether. Loss of N₂ from the initial cycloadduct **A** provides the carbonyl ylide **B** (eq 1, Table 1), which undergoes a subsequent established¹³ 1,3-dipolar cycloaddition with the tethered indole. Importantly, the diene and dienophile substituents complement and reinforce the [4 + 2] cycloaddition regioselectivity dictated by the linking tether, the intermediate 1,3-dipole is stabilized by the complementary substitution at the dipole termini, and the tethered 1,3-dipolarophile (indole) complements the [3 + 2] cycloaddition regioselectivity that is dictated by the linker tether. The relative stereochemistry in each cycloadduct is controlled by a combination of (1) the dienophile geometry and (2) an exclusive *endo* indole [3 + 2] cycloaddition¹³ sterically directed to the α -face opposite the newly formed fused lactam. This *endo* diastereoselection for the 1,3-dipolar cycloaddition may be attributed to a conformational (strain) preference dictated by the dipolarophile tether since it mirrors the relative energy of the four possible

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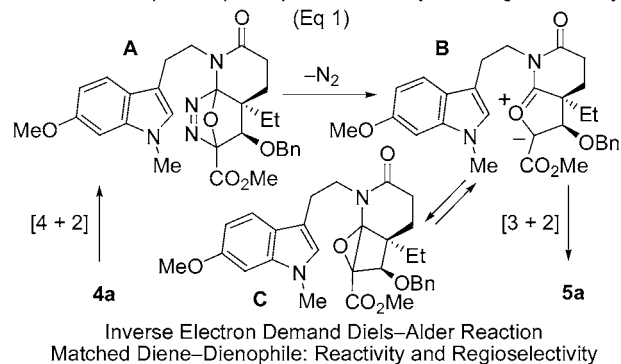
(11) Takano, S.; Shishido, K.; Matsuzaka, J.; Sato, M.; Ogasawara, K. *Heterocycles* **1979**, *13*, 307. An improved preparation is detailed in Supporting Information.

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(13) Padwa, A.; Price, A. T. *J. Org. Chem.* **1998**, *63*, 556; **1995**, *60*, 6258. Interestingly, intermolecular [3 + 2] variants proceed with indole *exo* cycloaddition directed to an analogous α -face, see: Muthusamy, S.; Gunanathan, C.; Babu, S. A. *Tetrahedron Lett.* **2001**, *42*, 523.

Table 1. Cycloaddition Concentration Dependence

1,3-Dipolar Cycloaddition of Stabilized Carbonyl Ylide
Matched 1,3-Dipole–Dipolarophile: Reactivity and Regioselectivity
(Eq 1)



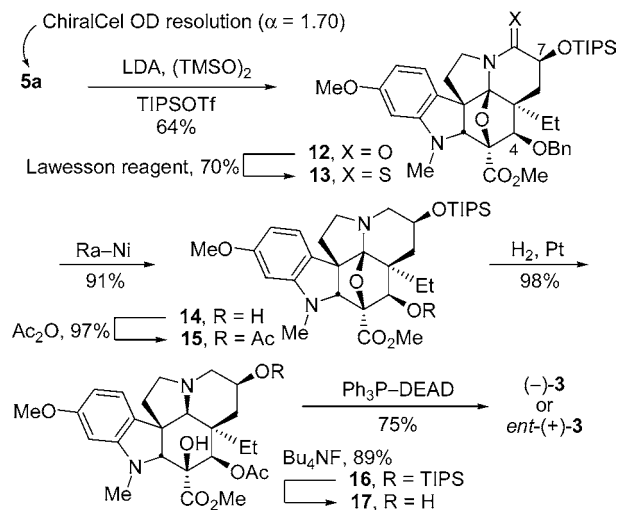
compound	concn (mM)	% yield 5a or 5b
4a ^a	5	27–34
4a ^a	1	43
4a ^a	0.1	50
4a ^a	0.05	53
4b ^b	100	38
4b ^b	50	58
4b ^b	10	86
4b ^b	5	90
4b ^b	1	99

^a Condition: 230 °C, TIPB, 90 h. ^b Condition: 230 °C, TIPB, 20 h.

products.¹⁰ The stereochemical assignments for **4a** and **4b** were based initially on their ¹H NMR spectroscopic properties and unambiguously established by X-ray.¹⁴ Thus, the cycloaddition cascade of either **4a** and **4b** provides complete control of the intrinsic stereochemistry found in the pentacyclic skeleton of the *Aspidosperma* alkaloids, establishing all six stereocenters about the central six-membered ring and was designed to introduce essentially all the functionality found in **3**. The distinction in the two cycloaddition cascades is that **4a** permits the direct introduction of the naturally occurring C4 OAc β -stereochemistry, whereas **4b** provides the C4 epimer, requiring a subsequent inversion of configuration at this center. Although substrate **4a** directly provides the preferred cycloadduct **5a** for the use in the synthesis of **3**, it proved to be more difficult to implement. The cyclization of **4a** occurs in excellent yield when warmed in triisopropylbenzene (TIPB), affording **5a** as a single diastereomer (Figure 2). Initial attempts to cyclize **4a** provided **5a** in low yield (<30% at >5 mM), and was in contrast to the cyclization of the **4b**, which provides the C4 diastereomer (84–99%). However, simple dilution of the reaction mixture led to improved yields (up to 53%). A study of this concentration effect is illustrated in Table 1 for both **4a** and **4b**, where a rather dramatic relationship between concentration and yield was found, especially for **4a**, suggesting that

a bimolecular 1,3-dipolar cycloaddition reaction of **4** may compete with the intramolecular cycloaddition cascade at the higher reaction concentrations. More significantly, we observed that the [4 + 2] cycloaddition is now the fast step in the reaction cascade and that the subsequent [3 + 2] cycloaddition is the slow step for **4a**, a reversal of what is observed with **4b** and other typical substrates.¹⁰ The net consequence is that longer reaction times and/or more vigorous reaction conditions, in conjunction with the use of a dilute reaction concentration, led to substantial improvements in the conversion of **4a**. The origin of the distinctions in the slow step of the cycloaddition cascade **4a** versus **4b** is not yet clear. The 1,3-dipolar cycloaddition transition state for **4b** embodies the more serious steric interactions disfavoring the indole endo approach on the α -face of the 1,3-dipole (Figure 2), yet it progresses with a greater facility than that of **4a**. It appears that the transition state for the 1,3-dipolar cycloaddition derived from **4a** suffers a destabilizing electrostatic interaction of its central oxygen with the (Z)-OBn substituent (Figure 2) that decelerates the reaction and/or that the (E)-OBn substituent of **4b** stabilizes its transition state (transition state anomeric effect). However, it is also possible that the preferred stereochemistry of the corresponding cyclobutene epoxide **C** or their relative stability, a potential intermediate and reversible source of the 1,3-dipole, may dictate the relative ease of the 1,3-dipolar cycloaddition and studies to probe such questions are in progress.

Although unanticipated, we found that the enantiomers of **5a** could be easily separated on a semipreparative Chiralcel OD column (30% *i*-PrOH/hexanes, 2 cm \times 25 cm) with a remarkable efficiency (α = 1.70, t_R = 15.1 and 25.6 min, 10 mL/min), providing access to either enantiomer on a preparatively useful scale (40–100 mg/injection). α -Hydroxylation of **5a** was achieved best by treatment of the lactam enolate with TMSO-OTMS and was followed by a direct quench with TIPSOTf providing **12** (56–64%), Scheme 2 (natural enantiomer shown). The stereochemistry

Scheme 2

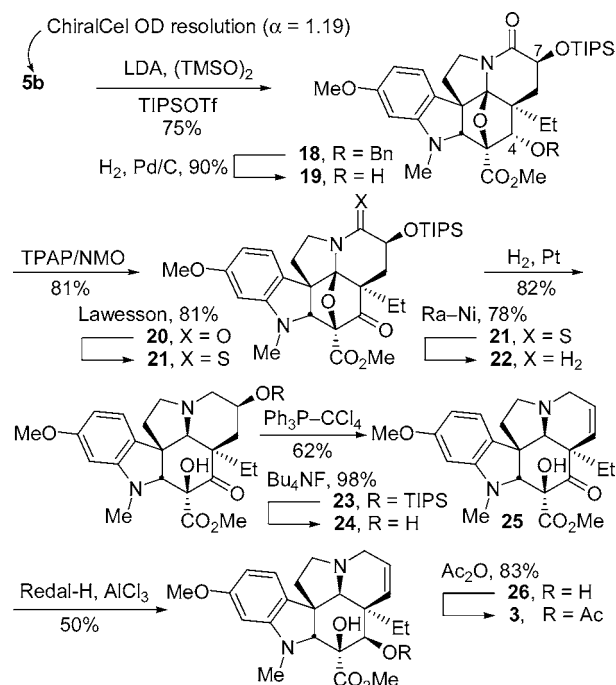
(14) X-ray crystal structures of **5a** (CCDC 253429), **5b** (CCDC 253430), the C7 *p*-bromobenzoate of **12** (CCDC 255976), and the C7 free alcohol of **18** (CCDC 253428) have been deposited with the Cambridge Crystallographic Data Centre.

of the α -hydroxylation was clear from the ^1H NMR of **12** (C7-H, $J = 5.5, 11.7$ Hz) and unambiguously determined by X-ray of the corresponding *p*-bromobenzoate.¹⁴ Conversion of **12** to thioamide **13** (70%) with Lawesson's reagent, reductive desulfurization with Raney Ni conducted under conditions (15 h, 23 °C) that also served to cleave the benzyl ether provided **14** (91%), and subsequent acetylation of the resulting secondary alcohol afforded **15** (97%). Diastereoselective reductive cleavage of the oxido bridge upon catalytic hydrogenation (45 psi H_2 , PtO_2 , 50% MeOH-EtOAc) with reduction of the intermediate imminium ion from the α -face provided **16** (98%), analogous to observations first made by Padwa,¹³ and silyl ether cleavage (Bu_4NF , 89%) and subsequent secondary alcohol activation and elimination of **17** (Ph_3P , DEAD, THF, 23 °C) provided either (–)- or *ent*(+)-vindoline (75%) identical in all respects with authentic material. The final conversion of **17** to **3** enlisting a Mitsunobu activation of the secondary alcohol for elimination may proceed via an intermediate aziridinium cation and relies on the reagent-derived base ($\text{EtO}_2\text{CNHN}^-\text{CO}_2\text{Et}$) to promote the regioselective elimination. This protocol proved much more effective and reproducible than alternative procedures that enlist reagents (e.g., $\text{Ph}_3\text{P-CCl}_4$)¹⁵ that generate reactive nucleophiles (e.g., Cl^-) that can compete with the elimination reaction.

A second total synthesis of vindoline was accomplished utilizing cycloadduct **5b** and was conducted while efforts to secure **5a** were underway (Scheme 3). The advantage is that the key cycloaddition cascade proceeds with greater facility under milder conditions and in higher conversions (>95%), albeit in a route requiring inversion of the C4 stereochemistry. Thus, α -hydroxylation of **5b** (LDA, TMSO-OTMS) followed by in situ treatment with TIPSOTf provided **18** in superb yield (75%). The stereochemistry of the intermediate alcohol, also obtained by a less effective reaction of the lactam enolate with Davis' reagent (40–50%), was established by ^1H NMR (C7-H, $J = 5.5, 12.1$ Hz) and confirmed by X-ray.¹⁴ C4-Alcohol deprotection (H_2 , Pd/C, 90%) and oxidation of **19** with TPAP/NMO provided **20** (81%). Thiolactam formation (Lawesson's reagent, toluene, 81%) and Raney Ni desulfurization of **21** (25 °C, 78%) preceded

(15) Kuehne, M. E.; Okuniewicz, F. J.; Kirkemo, C. L.; Bohnert, J. C. *J. Org. Chem.* **1982**, *47*, 1335.

Scheme 3



diastereoselective oxido bridge cleavage of **22** (H_2 , PtO_2 , MeOH , H^+)¹³ to furnish **23** (82%). TIPS ether cleavage (Bu_4NF , 98%) and treatment of **24** with $\text{Ph}_3\text{P-CCl}_4$ ¹⁵ led to activation and elimination of the C7 alcohol to provide **25** (62%). Following the protocol of Büchi,⁸ diastereoselective C4 carbonyl reduction of **25** (Redal-H, AlCl_3) and subsequent acetylation (Ac_2O , 83%) of deacetylvindoline (**26**) furnished vindoline (**3**).

Acknowledgment. We gratefully acknowledge the financial support of the National Institute of Health (CA42056) and the Skaggs Institute for Chemical Biology and wish to thank Y. Li for providing material at an intermediate stage of the studies.

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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