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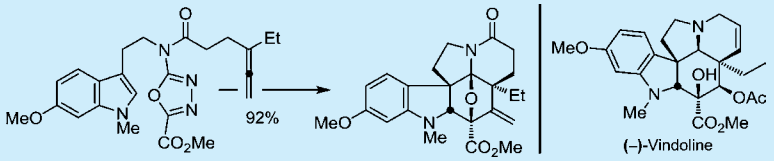
Total Synthesis of (−)-Vindoline and (+)-4-*epi*-Vindoline Based on a 1,3,4-Oxadiazole Tandem Intramolecular [4 + 2]/[3 + 2] Cycloaddition Cascade Initiated by an Allene Dienophile

Justin E. Sears, Timothy J. Barker, 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, United States

Supporting Information



ABSTRACT: It is reported that an allene dienophile can initiate a tandem intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of 1,3,4-oxadiazoles, that the intermediate cross-conjugated 1,3-dipole (a carbonyl ylide) can participate in an ensuing [3 + 2] dipolar cycloaddition in a remarkably effective manner, and that the reaction can be implemented to provide the core pentacyclic ring system of vindoline. Its discovery improves a previous total synthesis of (−)-vindoline and was used in a total synthesis of (+)-4-*epi*-vindoline and (+)-4-*epi*-vinblastine that additionally enlists an alternative series of late-stage transformations.

Vinblastine (**1**) along with vincristine (**2**) are the most widely recognized members of the bisindole Vinca alkaloids as a result of their long-standing clinical use as antitumor drugs (Figure 1).[1−4] In addition to being among the first natural

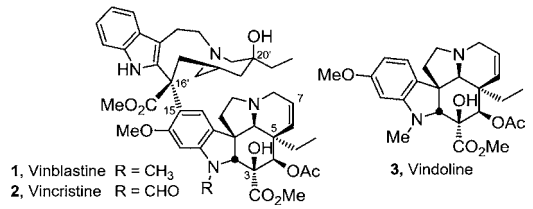


Figure 1. Natural product structures.

products whose structures were determined by X-ray crystallography, they were also among the first for which X-ray was used to establish their absolute configuration.[5] Vindoline (**3**), a major alkaloid of *Catharanthus roseus*, constitutes the most complex lower half of vinblastine and serves as both a biosynthetic[2] and synthetic[6] precursor to the natural product.

Previously, we reported the development of a concise total synthesis of (−)- and *ent*-(+)-vindoline[7−9] based on a tandem intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of a 1,3,4-oxadiazole[10−16] to assemble the pentacyclic skeleton with incorporation of all the necessary functionality and stereochemistry. The extension of this methodology to the preparation of a series of related natural products[17,18] and the subsequent development of an asymmetric total synthesis[19] of vindoline followed shortly thereafter. This work along with the use of a biomimetic Fe(III)-promoted coupling of vindoline with catharanthine[20] and the development of a subsequent in situ Fe(III)/$NaBH_4$-mediated free radical alkene oxidation for C20′-alcohol introduction[18,21−23] allowed for their single-step incorporation into total syntheses of vinblastine, related natural products including vincristine, and key analogues in routes as short as 8−12 steps.

These past efforts used the enol ether dienophiles **4** and **6** to initiate an oxadiazole [4 + 2]/[3 + 2] cycloaddition in which the resulting benzyl ether in the cascade cycloadduct **5** or **7** was used to install the vindoline C4-acetoxy group (Figure 2).[7] While **4** permitted the direct introduction of the naturally occurring C4-OAc stereochemistry, **6** provided the C4 epimer, requiring a subsequent inversion of configuration at this center. The cyclization of **6** proceeds in excellent yield when warmed in triisopropylbenzene (TIPB), affording **7** as a single diastereomer. In contrast, the cyclization of **4** proceeds more slowly and

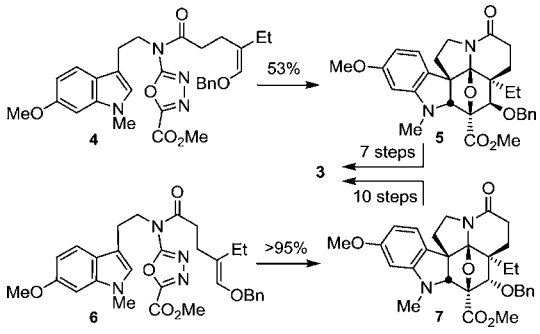


Figure 2. Key step in previous work.

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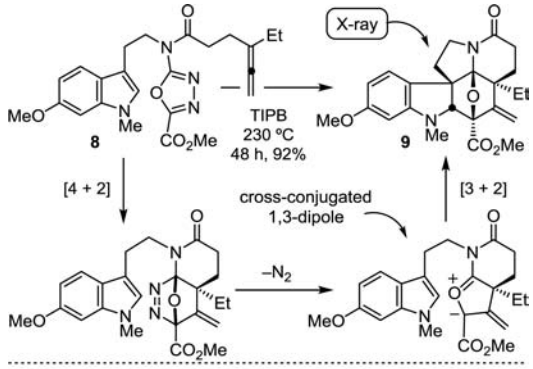
requires more dilute reaction conditions, providing the cycloadduct **5** (53%) as a single diastereomer albeit in more modest conversions. This results from a retarded rate of the ensuing [3 + 2] cycloaddition reaction derived from a destabilizing electrostatic interaction of the benzyl ether oxygen with the oxido bridge oxygen present with **5** but not **7**. Thus, although **4** directly provides the preferred cycloadduct **5** for use in the synthesis of vindoline, it proved less attractive to implement due to this less effective behavior in the cycloaddition cascade.

As a consequence of developments arising from their use in the discovery of several new classes of vinblastine analogues with properties that merit further study,[15−17,22] we have continued to explore improvements in this first generation synthesis of (−)-vindoline. Herein, we report an additional and remarkably effective tandem intramolecular [4 + 2]/[3 + 2] cycloaddition reaction in which an allene dienophile initiates the cycloaddition cascade. The resulting cascade cycloadduct, which bears an exocyclic olefin, permits the expedient, improved, and divergent syntheses of not only vindoline but also its C4 epimer. Recent exploration of substrates that bear alternative dienophiles and tethers provided the unanticipated discovery that an allene not only initiates the oxadiazole cycloaddition cascade but also provides the desired cycloadduct in superb yields (Scheme 1).

Scheme 1. Key [4 + 2]/[3 + 2] Cycloaddition Cascade



Cycloaddition Concentration Dependence

time (h)	concentration (mM)	% yield
24	1	83
24	2	75
24	10	19
24	20	17
9	2	67
48	2	92

All reactions performed at 230 °C, TIPB.

The initiating Diels−Alder reaction between the tethered allene and the electron-deficient 1,3,4-oxadiazole affords an initial cycloadduct that undergoes loss of N_2 to provide an unusual cross-conjugated 1,3-dipole (carbonyl ylide) that most might expect to be an unmanageable intermediate. The ensuing 1,3-dipolar cycloaddition reaction proceeds remarkably well and with a regioselectivity that is dictated by the linking tether, but reinforced by the intrinsic polarity of the reacting partners. Its exclusive diastereoselectivity is derived from an indole endo [3 + 2] cycloaddition, in which the dipolarophile is directed to the face opposite the newly formed six-membered ring. Four C−C bonds, three rings, five stereocenters, and the pentacyclic skeleton of vindoline are assembled in a single transformation.

The cycloaddition cascade reaction of **8** proceeds cleanly to provide a single diastereomer **9** whose structure was first established spectroscopically and confirmed with a single crystal X-ray structure determination.[24] Like the behavior of **4** and **6**,[7] the reaction exhibits a clear concentration dependence (Scheme 1) where an increase in the substrate concentration has the impact of lowering the yield. This is indicative of a competitive intermolecular reaction, presumably of the intermediate 1,3-dipole. When optimized (48 h), the reaction provided the single diastereomer **9** in excellent yield (92%), being competitive and faster than the reaction of **6** and exceeding that of **4**. Even when run for only 9 h, a 67% yield of **9** was obtained along with 30% of recovered **8** (96% yield brsm), indicating that the rate of reaction of **8** is substantially faster than either that of **4** or **6**.

Because of the cross-conjugated nature of the intermediate 1,3-dipole and the range of conceivable alternative reaction pathways available, its clean and effective participation in the indole [3 + 2] dipolar cycloaddition is especially remarkable. Computational studies (AM1) on the core 1,3-dipole indicate that the olefin is in conjugation with the 1,3-dipole, making the clean cycloaddition behavior of the intermediate that much more significant (Figure 3). Although not exhaustively searched, we were unable to locate a reported carbonyl ylide that involves such an unlikely cross-conjugated structure.

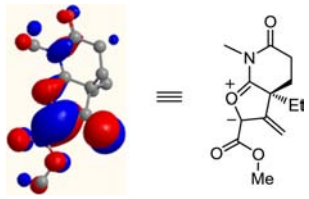


Figure 3. HOMO (AM1) of intermediate core 1,3-dipole.

Finally, the structure of the cascade cycloadduct **9**, in our opinion, is notable. The central six-membered ring formed under the reaction conditions contains four quaternary centers, three of which are contiguous, an oxido bridge, and an sp^2 hybridized carbon, making it both a strained and sterically congested oxanorbornane (see Supporting Information (SI) Figure S1).

Oxidation of the exocyclic double bond of cycloadduct **9**, which is surrounded by quaternary centers, initially proved challenging. Traditional methods such as ozonolysis and the Johnson−Lemieux oxidation failed to provide the desired ketone while the classical OsO_4-mediated dihydroxylation reaction conducted under Upjohn conditions (NMP/cat. OsO_4) failed to yield the desired diol, most likely the result of the steric hindrance surrounding this site. However, it was found that dihydroxylation using Corey's method (2:1 DMAP−OsO_4) provided the diol remarkably effectively (Scheme 2).[25] Typically, the intermediate diol **10** was not isolated and was carried directly into the subsequent oxidative cleavage reaction. Characterization of the intermediate diol **10** indicated that it is formed as a single diastereomer (81%), whose structure and stereochemistry were established in a single crystal X-ray structure determination.[24] Intermediate **10** is remarkable in that it bears five contiguous quaternary centers and 11 substituents around the central six-membered ring, which is an oxanorbornane that bears four endo axial and six total α-face (endo) substituents (Figure 4). Additionally, diol **10** possesses the same C4-alcohol stereochemistry found in vindoline that arises through dihydroxylation from the sterically less hindered exo face, making it an especially attractive intermediate with which to access vindoline and

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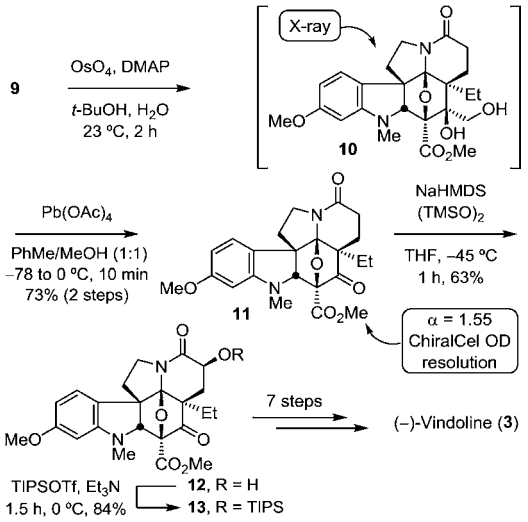
Scheme 2



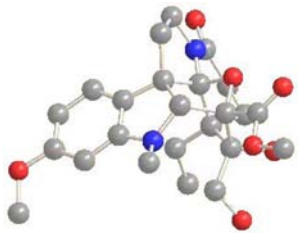


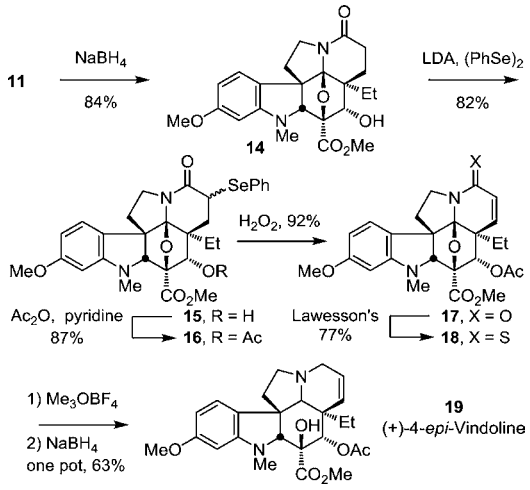
Figure 4. X-ray structure of **10**.

vinblastine analogues containing the additional C4-hydroxymethyl group or its derivatives.

Because of the surrounding steric constraints, diol **10** was not amenable to standard periodate-promoted oxidative cleavage methods ($NaIO_4$). Rather, $Pb(OAc)_4$ in toluene/methanol (1:1)[26] was employed to provide the ketone **11** in 73% yield over two steps (Scheme 2). After chromatographic resolution of the enantiomers of **11** (ChiralCel OD, α = 1.55, 15% *i*-PrOH/hexane), α-hydroxylation of the lactam enolate with $(TMSO)_2$ followed by in situ protection of **12** (TIPSOTf/Et_3N) provided silyl ether **13** (51%), which we previously converted to (−)-vindoline[7] formally completing an alternative synthesis that now enlists an initiating allene dienophile in a remarkable [4 + 2]/[3 + 2] cycloaddition cascade.

With straightforward access to ketone **11**, we also took the opportunity to prepare the C4 epimer of vindoline by total synthesis, exploring alternative late-stage conversions reversing the order of $\Delta^{6,7}$-double bond introduction, lactam carbonyl removal, and oxido bridge ring opening that could be applied to vindoline as well. Diastereoselective reduction of **11** with $NaBH_4$ ($MeOH/CH_2Cl_2$, −78 °C, 10 min, 84%) or $LiAlH(Ot\text{-}Bu)_3$ (THF, 0 °C, 3 h, 71%) proceeded smoothly to exclusively provide **14** (Scheme 3). Conversion of **14** to a mixture of α-selenides **15** (82%, ca. 8:1 β:α) was accomplished by treatment of the lactam enolate with diphenyl diselenide (LDA, THF, 3 h, −78 °C) without protection of the free alcohol. The mixture of selenides **15** was *O*-acetylated upon treatment with a 1:1 solution of Ac_2O and pyridine (cat. DMAP, 16 h, 23 °C, 87%) and subsequently subjected to treatment with excess aqueous H_2O_2 in THF (2 h, 23 °C) to provide the α,β-unsaturated lactam **17** (92%). These latter two reactions were most conveniently conducted without the intermediate purification of the

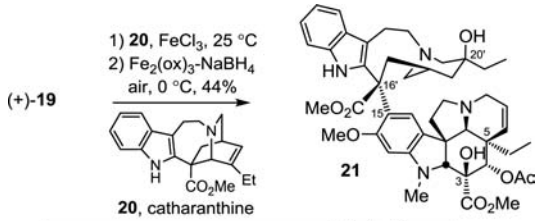
Scheme 3. Total Synthesis of (+)-4-*epi*-Vindoline



diasteromeric mixture of **16**, providing **17** in further improved overall yield (85% for two steps). Treatment of **17** with Lawesson's reagent (toluene, 1 h, 100 °C) provided thioamide **18** (77%), which was subjected to methylation with Meerwein's salt (Me_3OBF_4, CH_2Cl_2, 1 h, 23 °C) followed by $NaBH_4$ reduction (MeOH, 20 min, 0 °C) of the *S*-methyl iminium ion in the same vessel to provide the 4-*epi*-vindoline (**19**) cleanly (63%). To the best of our knowledge, not only does this represent the first total synthesis of (+)-4-*epi*-vindoline,[15b] but it was accomplished in an efficient manner, requiring only six isolated intermediates in route to **19** from the key cycloaddition cascade product.

For comparison purposes and with **19** in hand, the C4 epimer of vinblastine was prepared in a single additional step and used to establish the effect of this single change in the natural product. Following a procedure described earlier,[15b] Fe(III)-promoted coupling of (+)-**19** with catharanthine (**20**), which proceeds with complete control of the newly formed C16′ quaternary stereochemistry, and subsequent in situ $Fe_2(ox)_3/NaBH_4$-mediated free radical C20′ oxidation afforded 4-*epi*-vinblastine (**21**) and its C20′ isomer 4-*epi*-leurosidine (2:1 β:α diastereoselectivity) (Figure 5).

In cell growth inhibition assays against a mouse leukemia (L1210) and human colon cancer (HCT116) cell line that are used to initially examine vinblastine analogues, 4-*epi*-vinblastine (**21**) was found to be 10-fold less potent vinblastine and essentially equipotent with 4-desacetoxyvinblastine[18] that lacks the C4 acetoxy substituent altogether (Figure 5). These two



Compound	IC_{50} (nM) L1210	HCT116
1, vinblastine	6.0	6.8
21, 4-*epi*-vinblastine	75	80
4-desacetoxyvinblastine	60	60

Figure 5. Total synthesis and evaluation of 4-*epi*-vinblastine.

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comparisons indicate that both the presence and stereochemistry of the C4 acetoxy group significantly contribute to the activity of vinblastine. The origin of this substantial effect is not clear and must be subtle since this site does not interact with tubulin; rather, it forms an interface with solvent in the vinblastine bound complex (see SI Figure S2).

Herein, we have shown that an allene dienophile effectively initiates a 1,3,4-oxadiazole [4 + 2]/[3 + 2] cycloaddition cascade, that the intermediate cross-conjugated carbonyl ylide participates in the ensuing [3 + 2] dipolar cycloaddition in a remarkably effective fashion, and that the reaction can be implemented to provide the pentacyclic skeleton of vindoline in excellent yield. We used this reaction to improve our total synthesis of (−)-vindoline and to provide the first total synthesis of (+)-4-*epi*-vindoline, enlisting an alternative series of late-stage conversions. The latter was incorporated in a single step into 4-*epi*-vinblastine (13-step total synthesis) whose evaluation indicates that both the presence and stereochemistry of the C4 acetoxy group significantly contribute to the activity of vinblastine. In addition to the future use of the unique diol intermediate **10**, alternative alkene functionalization reactions with **9** can be envisioned to provide key additional analogues of vindoline and vinblastine and such efforts may be disclosed in due time.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02818.

Full experimental details are provided (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: boger@scripps.edu.

Notes

The authors declare no competing financial interest.

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