Published in final edited form as:

Acc Chem Res. 2016 February 16; 49(2): 241–251. doi:10.1021/acs.accounts.5b00510.

Tandem Intramolecular Diels–Alder/1,3-Dipolar Cycloaddition Cascade of 1,3,4-Oxadiazoles: Initial Scope and Applications

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Conspectus

A summary of the development and initial studies on the scope of a powerful tandem intramolecular $[4 + 2]/[3 + 2]$ cycloaddition cascade of 1,3,4-oxadiazoles is detailed and provides the foundation for its subsequent use in organic synthesis. Implemented with substrates in which both the initiating dienophile and subsequent dipolarophile are tethered to the 1,3,4-oxadiazoles, the studies expanded the scope of oxadiazoles that participate in the reaction cascade, permitted the use of differentiated dienophiles and dipolarophiles, extended their use to unsymmetrical dienophiles and dipolarophiles, provided exclusive control of the cycloaddition regioselectivities, and imposed exquisite control on the cycloaddition stereochemistry. As key reactivity and stereochemical features of the reactions were being defined, the cascade cycloaddition reaction was implemented in the total synthesis of a series of alkaloids including (–)-vindoline, (–)-vindorosine, the closely related natural products (+)-4-desacetoxyvindoline and (+)-4-desacetoxyvindorosine, natural minovine, (+)-*N*-methylaspidospermidine, (+)-spiegazzinine, (–)-aspidospermine, and a number of key analogues. Most recently it was used in the divergent total syntheses of (+)-fendleridine, (–)-kopsinine, (–)-kopsifoline D, and (–)-deoxoapodine, in which four different strategic bonds in four different classes of the hexacyclic alkaloids were formed from a common cascade cycloaddition intermediate. A large number of vindoline analogues were prepared by variations on the cascade cycloaddition reaction for single step incorporation into analogues of vinblastine. These structural changes to vindoline permitted both systematic alterations to the peripheral substituents as well as deep-seated changes to the core structure and embedded functionality of vinblastine not previously accessible. Although explored initially for accessing vindoline and vinblastine, the use of the cycloaddition cascade in the total synthesis of an impressive range of additional natural products illustrate the power of the methodology. Alternative tethering strategies for the cascade cycloaddition reaction, combined intramolecular and intermolecular variants of either the initiating Diels–Alder reaction or the subsequent carbonyl ylide 1,3-dipolar cycloaddition, an expanded examination of the tethered dipolarophile scope, and applications to additional natural product classes represent attractive areas for future work.

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The authors declare no competing financial interest.

Introduction

Cycloaddition reactions have long been powerful synthetic transformations in organic chemistry due to their ability to form multiple bonds with predictable stereochemistry, often providing access to the core cyclic structures of complex natural products. Tandem cycloadditions, or multiple cycloadditions that occur sequentially in the same reaction vessel, are especially powerful due to their ability to efficiently achieve high structural complexity, generating bridged or polycyclic structures containing several contiguous stereocenters, without the need to isolate intermediates before each subsequent reaction in the sequence.^{1–13} A special class of tandem cycloadditions that do not require the addition of reagents or modification of reaction conditions are deemed cascade cycloadditions.^{14–17} Cascade reactions are sometimes also referred to as domino reactions to emphasize that each step of the sequence depends on the functionality formed directly in the previous step.^{18–20}

In exploration of a new synthetic approach to vinblastine and vincristine, we developed a powerful cycloaddition cascade inspired by the structure of vindoline, the more complex lower half of vinblastine. This tandem intramolecular [4 + 2]/[3 + 2] cycloaddition provided the pentacyclic core in a single step, incorporating all the embedded heteroatoms, substituents, functional groups and necessary stereochemistry required for conversion not only to vindoline, but to a series of *Vinca* and *Aspidosperma* alkaloid natural products. Originally inspired by the potential development of sequential intramolecular inverse electron demand Diels–Alder reactions of unsymmetrically substituted 1,2,4,5-tetrazines,^{21–24} our approach ultimately enlisted an alternative cascade cycloaddition reaction of electron-deficient five-membered heterocyclic azadienes using 1,3,4-oxadiazoles in the initiating inverse electron demand Diels–Alder reaction.^{25,26} Although a limited number of reports had described the cycloadditions of electron-deficient 1,3,4-oxadiazoles, they typically employed symmetrical oxadiazoles bearing two strong electron-withdrawing substituents (CF₃, SO₂Et, CO₂Me) and all had been examined only in intermolecular reactions (Figure 1).^{27–47} Reactions of olefinic dienophiles were found to proceed through an initial [4 + 2] cycloadduct that loses N₂ to provide a carbonyl ylide that subsequently reacted again with the same olefin in a 1,3-dipolar cycloaddition reaction to provide only 2:1 cycloadducts, limiting their synthetic utility.

With the synthetic target vindoline (**1**) in mind, the tandem intramolecular Diels–Alder/1,3-dipolar cycloaddition reaction was implemented with substrates bearing both an initiating dienophile and a tethered indole to trap the *in situ* generated carbonyl ylide (Scheme 1). This work, representing the first examples of an intramolecular Diels–Alder and tandem intramolecular Diels–Alder/1,3-dipolar cycloaddition of 1,3,4-oxadiazoles, significantly expanded the scope of oxadiazoles that participate in the reaction cascade, permitted

differentiated dienophiles and dipolarophiles to be incorporated, imposed control onto the cycloaddition stereochemistry, and provided exclusive control of the cycloaddition regioselectivities, thereby enhancing the synthetic utility of such cycloaddition reactions.^{25,26} In the case highlighted in Scheme 1, a single diastereomer of the cycloaddition cascade product is produced in which the relative stereochemistry is set by a combination of: (1) the dienophile geometry, and (2) exclusive endo [3 + 2] cycloaddition of the tethered indole sterically directed to the α -face of the 1,3-dipole opposite the newly formed fused lactam.⁴⁸ Although it is tempting to attribute this latter endo cycloaddition diastereoselectivity as intrinsic to the [3 + 2] cycloaddition, comparable intermolecular reactions proceed with indole exo cycloaddition also directed to the sterically less hindered face.⁴⁹ The endo addition observed with the substrates examined to date may be attributed to a conformational preference for the 1,3-dipolar cycloaddition transition state that is dictated by the dipolarophile tether since it also reflects the relative strain energy of the four possible products.²⁶ The tandem cycloadditions construct three new rings with formation of four new C–C bonds and set all six stereocenters about the central six-membered ring in a single step typically without detection of a second diastereomer. Herein, we describe the key results of the initial exploration of the scope of this powerful intramolecular [4 + 2]/[3 + 2] cascade cycloaddition reaction and summarize its use to date in the total synthesis of natural products, including the total synthesis of analogues of vinblastine (**2**) and vincristine (**3**) that contain previously inaccessible deep-seated structural changes.

Scope of the Cycloaddition Cascade

Although the substitution of the oxadiazoles that were examined stabilize the intermediate 1,3-dipole, these substrates are less electron-deficient than those previously known to participate in the initiating inverse electron demand Diels–Alder reactions (Figure 2).^{25,26} This results in a reduction of intrinsic reactivity for the initial [4 + 2] reaction that is compensated for by its use in an intramolecular Diels–Alder reaction. *N*-Acylation of the oxadiazole C2 amino group was found to be required for [4 + 2] cycloaddition reactivity (Figure 2a), although there is little distinction whether *N*-acylation is incorporated into the dienophile or dipolarophile tether. Expectedly, the reaction rate increases as the electron-withdrawing properties of the activating amide increases ($R = \text{COCF}_3 > \text{Ac} \gg \text{H}$, Figure 2b). Moreover, the studies suggest that the tertiary amide is required, which readily adopts a *cis* amide conformation required for [4 + 2] cycloaddition, as substrates bearing a secondary amide failed to participate in the initiating Diels–Alder reaction (Figure 2c). Thus, while the presence of such a tertiary amide is central in the synthetic approach to vindoline where it served as the tether site for both the dienophile and dipolarophile, its use is more integral to the success of the cycloaddition than might be appreciated.

While the C5 methyl ester on the 1,3,4-oxadiazole was used to directly introduce the vindoline C3 methyl ester, other electron-withdrawing substituents effectively enhance the electron-deficient character of the oxadiazole, promoting the initiating inverse electron demand [4 + 2] cycloaddition reaction and stabilizing the intermediate 1,3-dipole. Thus, C5 electron-withdrawing substituents (CO_2Me , CONH_2 , CN) provided oxadiazoles that participate effectively in the cycloaddition cascade, substrates bearing conjugating (Ph)

substituents required more vigorous reaction conditions, and unactivating (Me, H) or electron-donating substituents (OMe) failed to support the tandem cycloaddition (Figure 3).

The relative ease of the tandem $[4 + 2]/[3 + 2]$ cycloaddition is consistent with the cascade being initiated by an inverse electron demand Diels–Alder reaction, but even unactivated and electron-deficient dienophiles can effectively initiate the reaction (Figure 4a). Notably, the addition of substituents to the tethered dienophile has a significant impact on the ease of cycloaddition (Figure 4b), and even the addition of activating substituents at the alkene terminus slows the reaction relative to the unsubstituted terminal alkene, independent of the site of substitution. The exceptions to these generalizations include trisubstituted enol ethers, which remain suitably reactive to initiate the cycloaddition cascade via an inverse electron demand Diels–Alder reaction. Impressively, the cycloadditions remain diastereoselective, providing a single detectable product. Although early studies failed to observe reactions initiated by trisubstituted dienophiles containing neutral and electron-withdrawing substituents,⁵⁰ recent studies have defined conditions where such substrates can be effectively used.⁵¹

While it is possible that an indole $[4 + 2]$ cycloaddition initiates the reaction cascade, attempts to detect such reactivity were not successful. If the reaction is prematurely worked up, only products derived from alkene $[4 + 2]$ cycloaddition were detected, and the substrate that bears both an indole dienophile and dipolarophile failed to undergo reaction, even under forcing conditions (Scheme 2).

In order to explore the requisite reactivity of the tethered indole and to probe deep-seated modifications that may be incorporated into the vindoline/vinblastine structure, a series of closely related tethered dipolarophiles were examined. As expected, it was determined that the rate-limiting step of these reactions is typically the initiating $[4 + 2]$ cycloaddition and that small differences in dipolarophile reactivity have no appreciable impact on the overall rate or yield (Figure 5a). Interestingly, tethered benzofurans and benzothiophenes (Figure 5a) participated effectively in the reaction cascade, while the corresponding furans and thiophenes (Figure 5b) failed to provide the analogous cycloadducts. The full scope of the tethered dipolarophiles that support the reaction has yet to be defined and represents a productive avenue for future studies.

Alterations in the dienophile and dipolarophile tether lengths were shown to be possible and impact the reaction efficiencies in a predictable manner.²⁶ Similarly, alternative tethering sites (e.g., C3 ester or C5 amide) create opportunities for the preparation of alternative fused ring systems and these likely represent productive avenues for future studies.²⁶

Applications in the Total Synthesis of Natural Products

These studies set the stage for development of a concise 11-step total synthesis of (–)-vindoline (**1**).^{52,53} The cycloaddition cascade of either **4a** and **4b** provided complete control of the intrinsic stereochemistry found in its pentacyclic skeleton, establishing all six stereocenters about the central six-membered ring and was designed to introduce essentially all the functionality found in **1** (Figure 6).

The distinction in the two cycloaddition reactions is that **4a** permits the direct introduction of the naturally occurring C4-OAc stereochemistry, whereas **4b** provides the C4 epimer, requiring an inversion of configuration at this center. Although **4a** directly provides the preferred cycloadduct **5a** for the use in the synthesis of **1**, it proved to be more difficult to implement. In fact, it was observed that the [4 + 2] cycloaddition was the fast step in the reaction cascade and the subsequent [3 + 2] cycloaddition was the slow step for **4a**, a reversal of what is observed with **4b** and other typical substrates. The net consequence is that use of longer reaction times, more vigorous reaction conditions, and a more dilute reaction concentration led to substantial improvements in the conversion of **4a**. This proved to be the result of the electronic character of the benzyloxy substituent of **4a** that decelerates the typically fast 1,3-dipolar cycloaddition. Thus, the transition state derived from **4a** suffers a destabilizing electrostatic interaction of its central oxygen with the (Z)-OBn substituent that decelerates the intramolecular dipolar cycloaddition reaction. With resolution of the cascade cycloadducts, both **5a** and **5b** permitted the expedient synthesis of (–)-**1** in 7 or 10 subsequent transformations, respectively.⁵²

The continued examination of functionalized dienophiles tethered to the oxadiazole revealed that an allene not only initiates the oxadiazole cycloaddition cascade, but provides the desired cycloadduct in superb yields (Figure 7).⁵⁴ The initiating Diels–Alder reaction affords an initial cycloadduct that undergoes loss of N₂ to provide an unusual cross-conjugated 1,3-dipole that most might judge to be an unmanageable intermediate. The ensuing 1,3-dipolar cycloaddition reaction proceeds remarkably well, providing **6** as a single diastereomer that results from an endo indole [3 + 2] cycloaddition. Corey dihydroxylation of **6** and subsequent Pb(OAc)₄ diol cleavage provided ketone **7** (73%). After chiral phase HPLC resolution of **7** (α = 1.55), α -hydroxylation followed by in situ silyl ether formation provided an intermediate that we had previously converted to (–)-vindoline, formally completing an alternative total synthesis. Ketone **7** was also converted to (+)-4-*epi*-vindoline in a remarkably efficient manner, requiring only six isolated intermediates from the key cycloaddition cascade product, and used to prepare 4-*epi*-vinblastine in a single additional step.⁵⁴

While the enantiomers of **5a** (α = 1.70) and **5b** (α = 1.19) as well as **7** (α = 1.55) were resolved by chiral phase HPLC to access both (–)-vindoline (natural) and *ent*-(+)-vindoline, an asymmetric synthesis was also developed based on an additional tandem [4 + 2]/[3 + 2] cycloaddition cascade in which the tether linking the initiating dienophile and oxadiazole bears a chiral substituent that sets the absolute stereochemistry of the remaining six stereocenters in the cascade cycloadduct (Figure 8).^{55,56} Cycloaddition of **8** proceeded cleanly, providing predominantly **9** in superb conversions, and only small amounts (0–13%) of a second diastereomer were occasionally isolated. The dienophile linking tether of **8** was reduced in length by one carbon relative to the earlier work, which not only permitted effective control of facial selectivity of the initiating Diels–Alder reaction but also allowed the reaction to be conducted under milder conditions than previously observed.⁵² The approach required that the activating acyl chain carbonyl reside in the dipolarophile tether and that the initiating Diels–Alder reaction provide a fused 5-membered ring, which must be suitably functionalized for subsequent ring expansion and introduction of the ^{6,7}-olefin.

Thus, the protected hydroxymethyl substituent of **8** not only effectively controls the stereochemical course of the cycloaddition cascade, but its use also provided two unique approaches to ring expansion.⁵⁶ The first approach relied on a hydrolytic ring expansion of an activated *N,O*-ketal that is generated from the primary alcohol, while the second enlisted an intermediate aziridinium ion in a thermodynamically controlled reversible ring opening reaction. Together, the asymmetric [4 + 2]/[3 + 2] cycloaddition reaction cascade along with two approaches to ring expansion provided two distinct, concise asymmetric total syntheses of (–)-vindoline (**1**).^{55,56}

The subsequent development of a biomimetic⁵⁷ Fe(III)-promoted coupling of vindoline with catharanthine^{58–60} allowed for their single step incorporation into total syntheses of vinblastine and related natural products (Figure 9). In addition to its use in the completion of the total syntheses of vinblastine (12 steps), vincristine, and a series of additional naturally occurring *Vinca* alkaloids, the approach also permitted the incorporation of vindoline analogues containing single site peripheral changes⁶¹ (Figure 9) as well as deep-seated changes to the vindoline core structure.⁶² As a result, a systematic exploration of the vindoline subunit structure of vinblastine was conducted, enlisting the cycloaddition cascade reaction to provide a series of vindoline analogues and their single step incorporation into the corresponding vinblastine analogues.

The introduction of alternative substitutions on the tethered dienophile allowed for systematic replacement of the vindoline C5 ethyl group, providing analogues that bear deep-seated structural changes at a site only accessible by total synthesis.⁶³ The alternative substituents were well-tolerated in the cycloaddition cascade, leading to the exclusive formation of one diastereomer in superb yield (66–95%) consistent with expectations^{26,52} (Figure 10a). When incorporated into vinblastine analogues through their single step coupling with catharanthine (5 steps from an early stage common intermediate), this series provided the first systematic exploration of the impact of this site on biological activity and revealed that it is exquisitely sensitive to the presence, size, and polarity of the C5 ethyl group.

Alteration of the length of either the dienophile or dipolarophile tether provided the opportunity to modify the vindoline 6,5-D,E ring core architecture, affording the 5,5-, 6,6- and reversed 5,6-membered DE ring systems (Figure 11a).⁶⁴ The 5,5-vindoline subunit analogue was accessed through an intermediate previously enlisted in the asymmetric synthesis of vindoline,⁵⁶ where a remarkably facile thermal deformylation reaction of **10** generated **11** directly (50%).⁶⁴ Presumably this unusual reaction occurs by reversible iminium ion formation followed by loss of formaldehyde to generate a stabilized singlet carbene that undergoes an insertion of the proximal C3 alcohol for reclosure of the *N,O*-ketal, affording the 5,5-D,E ring analogue of vindoline (Figure 11b). Increasing the length of the dipolarophile tether by one carbon and varying the length of the dienophile tether provided cycloadducts bearing the corresponding 6,5- and 6,6-DE ring system analogues. The vindoline analogues were found to be suitable substrates for the biomimetic Fe(III)-promoted coupling and subsequent HAT^{61,65} oxidation reaction, enabling access to vinblastine analogues that represent the largest departure from the structure of the vindoline subunit to date and that are not available from natural product sources. Most interesting in

this probe was that it was the analogues that bore the greatest departure from the natural products (**12** and **13**) that exhibited the best activity, matching that of the comparison natural products.⁶⁴ Unlike modifications to peripheral substituents, such core redesign is rarely explored in complex natural products, and was possible only because of the power of the oxadiazole cycloaddition cascade.

In the continued examination of key analogues of vinblastine, the scope of the key cycloaddition cascade was expanded to include substrates where the dienophile is constrained within a macrocycle, rendering the initiating [4 + 2] reaction transannular.⁶⁶ Expectedly, the macrocyclic oxadiazoles undergo the tandem cycloaddition cascade at temperatures substantially lower than those of the related intramolecular reactions,^{26,52} forming an impressive four rings, four carbon–carbon bonds, and six stereocenters at temperatures as low as 80 °C (Figure 12). The resulting cycloadducts provided the basis for the synthesis of unique vinblastine analogues containing deep-seated modifications at the metabolically labile C3/C4 centers of the natural product.⁶⁶

As key elements of the scope and stereochemical features of the reaction were defined, a series of related natural products of increasing complexity were prepared by total synthesis. A total synthesis of natural and *ent*-minovine was completed in which questions surrounding the optical rotation, racemization potential, optical purity, and absolute configuration of the natural product were resolved.⁵² The same intermediate, albeit in the enantiomeric series, was enlisted in the total synthesis of (+)-*N*-methylaspidospermidine, which not only constituted its first total synthesis but also served to confirm its absolute configuration⁵² (Figure 13a). Similarly, the first total syntheses of 4-desacetoxy-6,7-dihydrovindorosine and 4-desacetoxyvindorosine,⁵² a late stage biosynthetic intermediate for (–)-vindorosine, were conducted along with efforts that provided a concise 11-step total synthesis of (–)- and *ent*-(+)-vindorosine^{52,67} (Figure 13b). In parallel, a total synthesis of the vindoline penultimate biosynthetic precursor (+)-4-desacetoxyvindoline was disclosed, representing its first total synthesis and the first instance of its characterization. Additionally, total syntheses of (+)-6,7-dihydrovindoline and (+)-4-desacetoxy-6,7-dihydrovindoline were completed.

These studies were extended to the total synthesis of additional key members of the *Aspidosperma* alkaloids, (+)-spgazzinine and (–)-aspidospermine (Figure 14).⁶⁹ This strategy was especially suited for spgazzinine, whose C3 alcohol was directly introduced upon reduction of a stable cyanohydrin formed after reductive oxido bridge cleavage of a nitrile derived from such a cycloaddition cascade product. An added bonus of the approach is that late stage modification of a route needed to define the spgazzinine C3 alcohol stereochemistry also permitted a divergent synthesis of aspodospermine, entailing removal of the C3 alcohol. Significantly, this work constituted the first total synthesis of (+)-spgazzinine, serving to unambiguously assign its absolute configuration, and the first reported synthesis of (–)-aspidospermine that did not rely on a late-stage Fischer indole synthesis.⁶⁹

The cycloaddition cascade was also successfully implemented in the synthesis of alkaloids bearing more complex hexacyclic ring cores. The cycloadduct **15** derived from the tandem [4 + 2]/[3 + 2] cycloaddition cascade of 1,3,4-oxadiazole **14** served as an intermediate in the

divergent synthesis of members of four different classes of natural products^{70–72} (Figure 15). This approach relied on late-stage divergent formation of four different key strategic bonds uniquely embedded in each natural product core structure.

For (+)-fendleridine, the intrinsic oxidation state at C19 of **15** was exploited for closure of the tetrahydrofuran ring and with a modification that permits introduction of useful functionality (cyanohydrin) following cleavage of the oxido bridge.⁷⁰ The reversibly generated iminium ion derived from oxido bridge opening is flanked by two quaternary centers, facilitating trap by the pendant alcohol (Scheme 3).

The approach to kopsinine enlisted a late stage C21–C2 bond formation that fundamentally differs from prior approaches.⁷¹ A SmI₂-promoted transannular cyclization reaction provided the bicyclo[2.2.2]octane central to the kopsinine ring system. This unique transformation resulted from radical-mediated conjugate addition cyclization of the methyl dithiocarbonate followed by kinetic protonation of the further reduced ester enolate from the less hindered convex face (Scheme 4). Alternatively, the primary alcohol could be converted to the corresponding iodide and shown to undergo the SmI₂-promoted transannular cyclization reaction even more effectively (85%).⁷³

In the approach to (–)-kopsifoline D, a late-stage C21–C3 bond formation via a transannular enamide alkylation of an alcohol-derived C21 iodide was developed (Scheme 5) to complete the assemblage of the kopsifoline skeleton in a route that directly provides the natural product in its final indolenine oxidation state.⁷² This approach mimics what is the likely biosynthesis of the kopsifolines and represents the first total synthesis of a naturally occurring kopsifoline.

In complementary efforts, silyl ether deprotection prior to lactam carbonyl removal permitted C21–O–C6 bond formation by conjugate addition of the primary alcohol (Scheme 6), effecting closure of the tetrahydrofuran ring of (–)-deoxoapodine. This work represented the first synthesis of (–)-deoxoapodine in optically active form, confirming the absolute configuration assignment.⁷²

These combined efforts represent the total syntheses of members of four different classes of natural products from a common intermediate, the cycloaddition cascade product of 1,3,4-oxadiazole **14**, functionalized for late-stage formation of four different key strategic bonds uniquely embedded in each natural product core structure.

Conclusions and Outlook

Inspired by the structure of vindoline, the development of a powerful tandem intramolecular Diels–Alder/1,3-dipolar cycloaddition cascade of 1,3,4-oxadiazoles was conducted. Although its full scope remains to be established, its use in the total synthesis of vindoline, an extensive series of analogues, a set of related natural products including vindorosine, their incorporation into total syntheses of vinblastine and an extensive series of analogues, and an impressive range of additional natural products illustrate the power of the methodology. Alternative tethering strategies for the cascade cycloaddition reaction, combined intramolecular and intermolecular variants of either the initiating Diels–Alder

reaction or the subsequent carbonyl ylide 1,3-dipolar cycloaddition, an expanded examination of the tethered dipolarophile scope, and applications to additional natural product classes represent attractive areas for future work.

Acknowledgments

We gratefully acknowledge the financial support of the National Institute of Health (CA115526 and CA042056, DLB).

Biographies

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Figure 1.
Tandem [4 + 2]/[3 + 2] cascade cycloaddition reaction of 1,3,4-oxadiazole.

Figure 2.

Impact of the amide substituent and alternatives to the amide.

Figure 3.
Impact of oxadiazole electron-withdrawing substituent.

Figure 4.
Impact of initiating dienophile substitution.

Figure 5.
Tethered dipolarophile.

- *E* faster than *Z*
- Forms 3 rings
4 C-C bonds
6 stereocenters
4 quaternary centers

dipolar cycloaddition

- α -face opposite fused lactam
- *endo* indole transition state

Figure 6.
First generation total synthesis of (-)-vindoline.

Figure 7.
Additional total synthesis of (-)-vindoline.

Figure 8.
Asymmetric total synthesis of (–)-vindoline.

Figure 9.

Representative analogues probing vinblastine substituents.

Figure 10.

Systematic examination of the embedded vinblastine C5 ethyl substituent.

Figure 11.
Modification of the vindoline core structure in vinblastine.

Figure 12.

Initiation of reaction cascade with a transannular [4 + 2] cycloaddition reaction.

Figure 13.

First and second generation total syntheses of (–)-vindorosine and related natural products.

Figure 14.
Divergent total synthesis of (+)-spegazzinine and (-)-aspidospermine.

Figure 15.
Divergent total synthesis of members of four different alkaloid classes from a common cascade cycloaddition product.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.