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Asymmetric Total Synthesis of Vindoline

Daisuke Kato, **Yoshikazu Sasaki**, 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 asymmetric total synthesis of (−)-vindoline (**1**) is detailed based on a tandem intramolecular [4+2]/[3+2] cycloaddition cascade of a 1,3,4-oxadiazole inspired by the natural product structure, in which the tether linking the initiating dienophile and oxadiazole bears a chiral substituent that controls the facial selectivity of the initiating Diels–Alder reaction and sets absolute stereochemistry of the remaining six stereocenters in the cascade cycloadduct. This key reaction introduces three rings and four C–C bonds central to the pentacyclic ring system setting all six stereocenters and introducing essentially all the functionality found in the natural product in a single step. Implementation of the approach also required the development of a unique ring expansion reaction to provide a 6-membered ring suitably functionalized for introduction of the $\Delta^{6,7}$-double bond found in the core structure of vindoline and defined our use of a protected hydroxymethyl group as the substituent used to control the stereochemical course of the cycloaddition cascade.

Vindoline (**1**),[1,2] a major alkaloid of *Cantharanthus roseus*, constitutes the more complex lower half of vinblastine (**2**)[2–5] and serves as both a biosynthetic[3,4] and synthetic[6,7] precursor to this important natural product (Figure 1). We recently reported the development of a concise total synthesis of (−)- and *ent*-(+)- vindoline8–10 enlisting an intramolecular tandem [4+2]/[3 +2] cycloaddition cascade of 1,3,4-oxadiazoles11 with resolution of a key intermediate, its extension to the preparation of a series of related natural products including vindorosine,10, 12 and the subsequent development of a biomimetic Fe(III)-promoted coupling with catharanthine for their single step incorporation into total syntheses of vinblastine and related natural products.6f Herein, we report the development of an asymmetric total synthesis of (−)-vindoline based on an additional implementation of the tandem [4+2]/[3+2] cycloaddition reaction in which the tether linking the initiating dienophile and oxadiazole bears a chiral substituent that sets absolute stereochemistry of the remaining six stereocenters in the cascade cycloadduct. Relative to our earlier work,10 the dienophile linking tether was reduced in length by one carbon permitting the effective control of the facial selectivity of the initiating Diels–Alder reaction and subsequent transmission of the attached substituent stereochemistry throughout the newly constructed pentacyclic ring system that was not observed in our studies with a four atom tether to the initiating dienophile.10 Moreover, this insured that the initiating Diels–Alder reaction could be conducted under milder conditions than previously observed.11 The approach required that the activating acyl chain carbonyl now reside in the dipolarophile tether and that the [4+2] cycloaddition afford a fused 5-membered versus 6-membered ring. A subsequent, unique ring expansion reaction was developed to provide a 6-membered ring suitably functionalized for introduction of the $\Delta^{6,7}$-double bond found in the core structure of vindoline and defined our use of a protected hydroxymethyl group as the substituent used to control the stereochemical course of the cycloaddition cascade.

boger@scripps.edu.

Supporting Information Available: Full experimental details are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The most important question addressed in initial studies was the stereochemical fate of the key cycloaddition cascade. Accordingly, substrate **13** was prepared and examined in detail. Although **13** lacks the aryl methoxy substituent required for the synthesis of vindoline, it was judged to be an ideal surrogate for examination of the key cycloaddition reaction. The side chain chirality was set using aspartic acid as the starting material (Scheme 1, both enantiomers prepared, natural enantiomer series shown). Teoc protection of $_D$-H_2N-Asp(OBn)-OH (TeocOSu, quant.) followed by mixed anhydride formation (*i*-BuOCOCl, NMM, DME, −15 °C) and reduction ($NaBH_4$, H_2O) provided the alcohol **5** (91%), which was protected as its MOM ether **6** (MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 84%). Benzyl ester hydrogenolysis (H_2, 10% Pd/C, THF), coupling of the crude carboxylic acid with *N*,*O*-dimethylhydroxylamine (EDCI, DMAP, *i*-Pr_2NEt, CH_2Cl_2, 94% from **6**), and reaction of the Weinreb amide **7** with EtMgBr (3 equiv, 3 equiv of $CeCl_3$, THF, 0 °C, 1 h, quant.)[13] cleanly provided the ethyl ketone **8**.

Wittig olefination of **8** with Ph_3P=CHOBn provided a 1:1 mixture of the separable (*E*) and (*Z*) enol ethers **9**. Teoc deprotection (Bu_4NF) and treatment of the liberated amine with carbonyldiimidazole (CDI) afforded **10** (86%, two steps) that was converted to the oxadiazole precursor **12** by treatment with methyl oxalylhydrazide[14] in the presence of HOAc (78%) and cyclization of **11** to form the corresponding oxadiazole (TsCl, Et_3N, CH_2Cl_2, 94%). Coupling of **12** with (1-methylindol-3-yl)-2-acetic acid provided the substrate **13** with which the initial examination of the cycloaddition cascade was conducted.

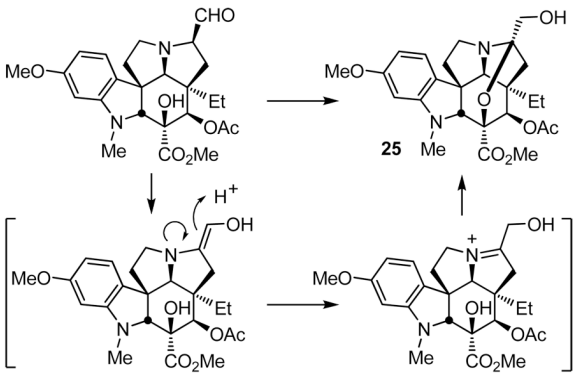
Cyclization of **13** proceeded effectively providing essentially or predominantly a single cascade cyloaddition diastereomer **14** in superb conversions (72%, xylene, 145–150 °C, 10 h) and only small amounts (0–13%) of a second diastereomer were detected, Scheme 2. The temperature required to initiate the cycloaddition cascade is lower (145 vs 180 °C) and the reaction time required for complete reaction is shorter (10 vs 24 h) than those observed with substrates bearing a longer dienophile tether.[10]

Diastereoselective reductive cleavage of the oxido bridge was effected by treatment with $NaCNBH_3$ (2 equiv, 20% HOAc–*i*-PrOH, 0–25 °C, 40 min, 94%) in a reaction that proceeds by acid-catalyzed generation of an acyliminium ion flanked by two quaternary centers that is reduced by hydride addition to the less hindered convex face, and provided **15** whose structure and stereochemistry were confirmed in a single crystal X-ray structure determination.[15] Following initial studies characterizing the cascade cycloaddition reaction of **13**, it proved most convenient to run the cycloaddition and subsequent reductive oxido bridge cleavage without the intermediate purification of **14**, which proved sensitive to silica gel exposure, providing **15** directly in good overall conversions (57–70% for two steps).

The reaction cascade is initiated by [4+2] cycloaddition of the 1,3,4-oxadiazole with the tethered electron-rich enol ether whose reactivity and regioselectivity are matched to react with the electron-deficient oxadiazole in an inverse electron demand Diels–Alder reaction (Figure 1). Loss of N_2 from the initial cycloadduct provides a carbonyl ylide, which undergoes a subsequent 1,3-dipolar cycloaddition with the tethered indole.[16] The diene and dienophile substituents 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 intrinsic regioselectivity of the attached dipolarophile (indole) complements the [3+2] cycloaddition regioselectivity that is set by its linking chain. The dienophile tether substituent effectively controls the facial selectivity of the initiating [4+2] cycloaddition reaction dictating that the protected hydroxylmethyl group at C7 and the C5 ethyl group reside trans to one another on the newly formed 5-membered ring avoiding a cis pseudodiaxial-1,3-interaction on the sterically more congested concave face of the transition state leading to the initial [4+2] cycloadduct. This establishes the absolute stereochemistry at C5, which in turn is transmitted throughout the cascade cycloadduct where the remaining relative stereochemistry

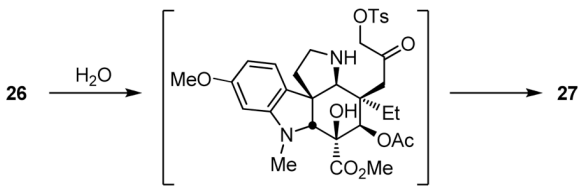
is controlled by a combination of the dienophile geometry (C4 and C5 stereochemistry) and an endo indole [3+2] cycloaddition sterically directed to the face of the 1,3-dipole opposite the newly formed 5-membered ring.[10–12] The minor diastereomer occasionally observed in the cycloaddition of **13** appears to be derived from endo indole [3+2] cycloaddition on the same face of the 1,3-dipole as the newly formed 5-membered ring (C2/C11 diastereomer) suggesting the facial selectivity for the initiating Diels–Alder reaction is >20:1 (detection limits).[17]

The substrate **16**, required for the synthesis of vindoline and bearing the indole methoxy group participated in the cycloaddition cascade (130 °C, 8 h and 175 °C, 8 h, xylene) in an analogous fashion and, although the initial cascade cycloadduct **17** was isolated and characterized, it was most conveniently subjected to reductive oxido bridge cleavage ($NaCNBH_3$, 10% HOAc/*i*-PrOH) prior to purification providing **18** directly (55% for two steps, Scheme 2). The product **18** was converted to the key intermediate **22** by benzyl ether hydrogenolysis (91%), oxidation of the free alcohol **19** (DMP, pyridine–CH_2Cl_2, 0 °C, 3 h, 76%) and diastereoselective ketone reduction ($LiAlH(O^tBu)_3$, THF, 0 °C, 10 h, 87%, 30:1 dr) from the less hindered convex face of **20**, followed by C4 alcohol **21** acetylation (Ac_2O, DMAP, pyridine, 95%) to provide **22** (Scheme 2). *O*-Methylation and reductive removal of the lactam carbonyl (MeOTf, 2,6-di-*t*butylpyridine, CH_2Cl_2, 25 °C, 2 h; $NaBH_4$, MeOH, 25 °C, 5 min) followed by MOM ether deprotection (HCl, MeOH, 25 °C, 16 h) liberated the primary alcohol **24** (85% for two steps from **22**). Oxidation (3 equiv of SO_3–Py, 3 equiv of Et_3N, CH_2Cl_2/DMSO, 25 °C, 1–2 h) of **24** provided an unstable α-aminoaldehyde that not only rapidly epimerized, but was found to be prone to hydrate and enol formation. Moreover, we found that simply exposing the crude aldehyde to silica gel in the presence of Et_3N (1% Et_3N/EtOAc) in the course of conventional purification led to clean conversion to the stable *N*,*O*-ketal **25** (85%), equation 1.



(1)

Formation of the primary tosylate **26** (TsCl, DMAP, Et_3N, CH_2Cl_2, 25 °C, 16 h, 93%) and its subjection to conditions developed for ring expansion[18] (NaOAc, dioxane–H_2O, 70 °C) provided the key 6-membered ring ketone **17** (61%). Although several mechanistic possibilities can be envisioned for this transformation, some of which proceed through an aziridiniumion, it is most simply and formally represented as hydrolysis of the *N*,*O*-ketal to release a reactive α-tosyloxymethyl ketone followed by its intramolecular *N*-alkylation to provide the 6-membered ketone **17** (equation 2).



(2)

Diastereoselective reduction of **27** (L-selectride, THF, −78 °C, 0.5 h) provided the penultimate secondary alcohol **28** (91%, >30:1 dr),[12c] which turn underwent regioselective elimination as previously described10 to provide vindoline (**1**) upon Mitsunobu activation in the absence of added nucleophiles, Scheme 2.[19]

Exploration of additional means to effect the key ring expansion reaction, extensions to the preparation of additional Aspidosperma alkaloids and key vindoline analogues, and their incorporation (e.g., **24** and **28**) into vinblastine analogues are in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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17. The substrate **13** bearing the (*Z*)-enol ether also participates in the cycloaddition cascade, but not as effectively as the (*E*)-enol ether (51–57% vs 72%) and requires more dilute reaction conditions (0.1 vs 1–5 mM).
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19. Abbreviations: EDCI = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; DMP = Dess-Martin periodinane; MOM = methoxymethyl; DMAP = 4-dimethylaminopyridine; DMSO = dimethylsulfoxide; NMM = *N*-methylmorpholine; Teoc = 2-(trimethylsilyl)ethoxycarbonyl.

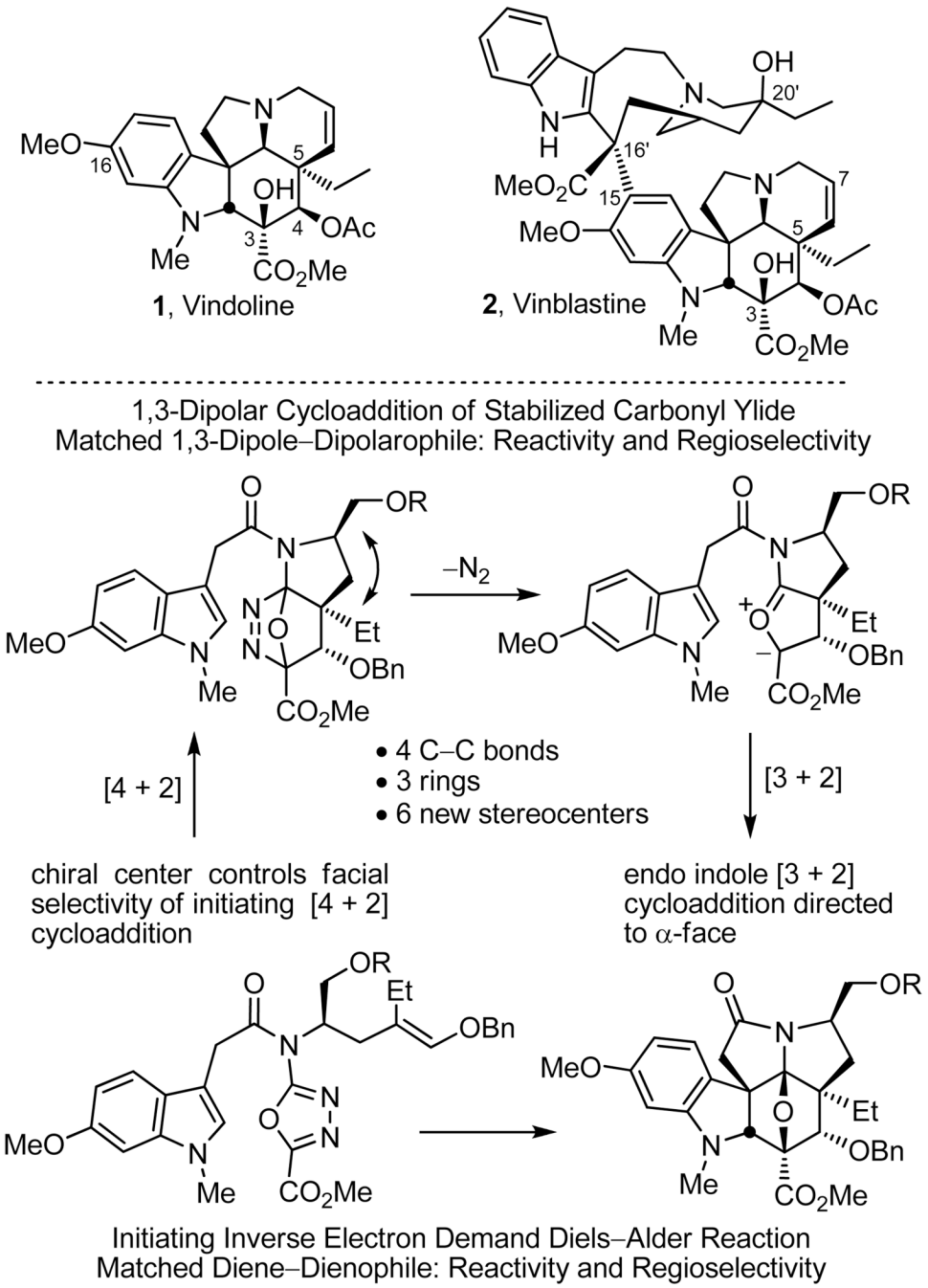
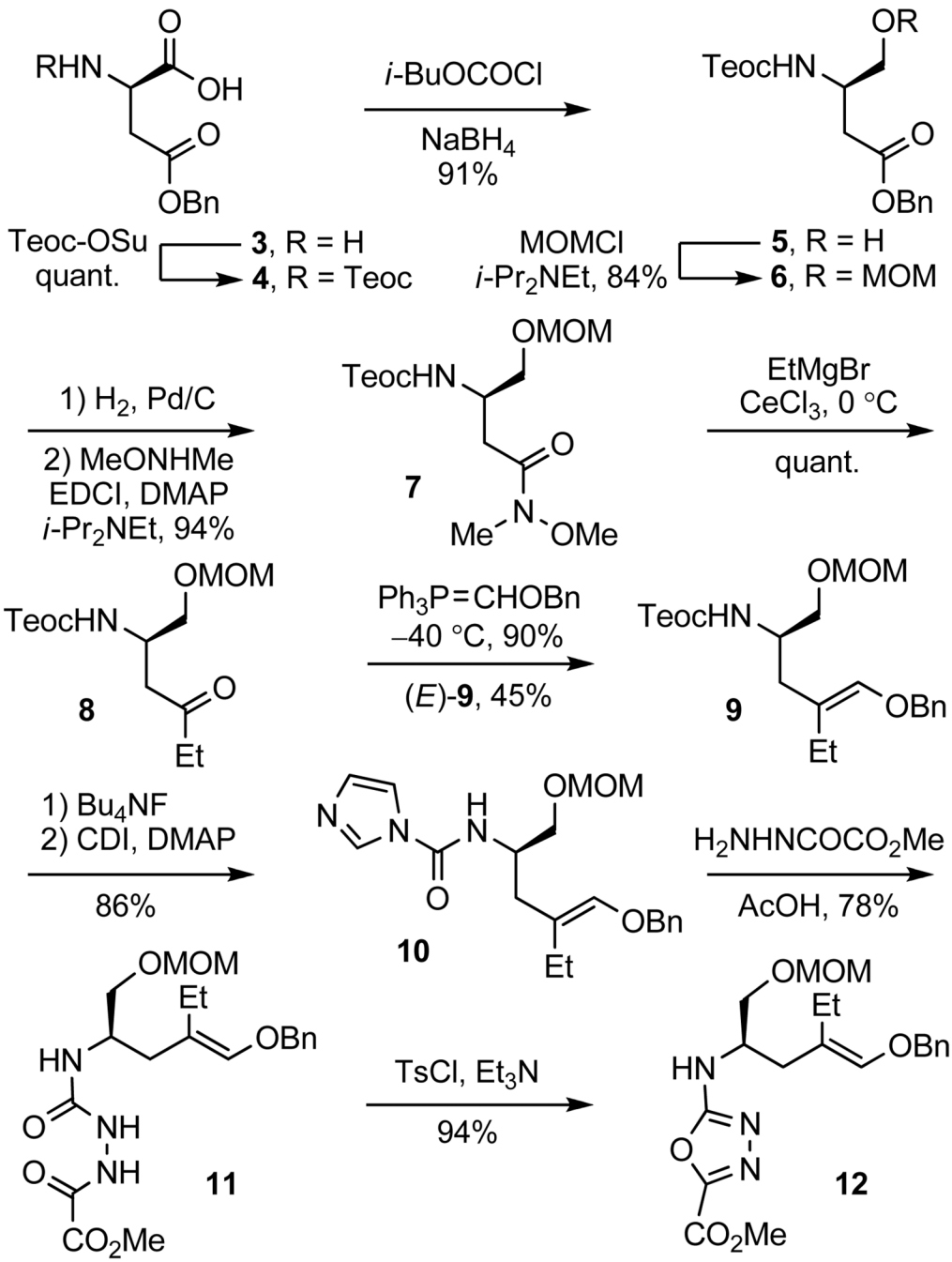
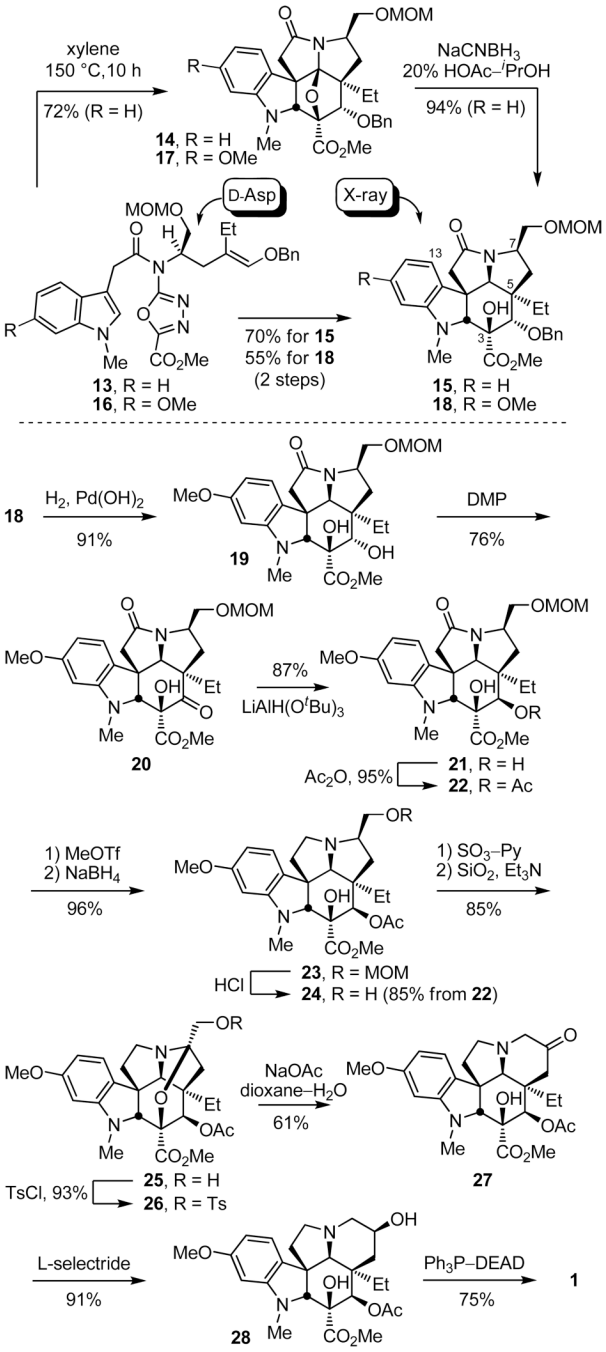


Figure 1.
Natural product and key cycloaddition cascade.



Scheme 1.



Scheme 2.