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Total Synthesis of (−)- and *ent*-(+)-Vindoline and Related Alkaloids

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Abstract

A concise 11-step total synthesis of (−)- and *ent*-(+)-vindoline (**3**) is detailed based on a unique tandem intramolecular [4+2]/[3+2] cycloaddition cascade of a 1,3,4-oxadiazole inspired by the natural product structure, in which three rings and four C–C bonds are formed central to the characteristic pentacyclic ring system setting all six stereocenters and introducing essentially all the functionality found in the natural product in a single step. 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 including both enantiomers of minovine (**4**), 4-desacetoxy-6,7-dihydrovindorosine (**5**), 4-desacetoxyvindorosine (**6**), and vindorosine (**7**) as well as N-methylaspidospermidine (**11**). Subsequent extensions of the approach provided both enantiomers of 6,7-dihydrovindoline (**8**), 4-desacetoxyvindoline (**9**), and 4-desacetoxy-6,7-dihydrovindoline (**10**).

Introduction

Vinblastine (**1**) and vincristine (**2**) constitute the most widely recognized members of a class of bisindole alkaloids as a result of their clinical use as antitumor 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] In addition to being among the first natural products whose structures were determined by X-ray, they were also among the first for which X-ray of a heavy atom derivative was used to establish their absolute configuration.[4] Vindoline (**3**),[4,5] a major alkaloid of *Cantharanthus roseus*, constitutes the most complex half of vinblastine and serves as both a biosynthetic[2] and synthetic[6] precursor to the natural product.[7]

Herein, we provide full details of the development of an unusually concise total synthesis of (−)- and *ent*-(+)-vindoline[8-10] (**3**) in which the full pentacyclic skeleton complete with all substituents and all six stereocenters is created in a single step enlisting a tandem intramolecular [4+2]/[3+2] cycloaddition cascade of a 1,3,4-oxadiazole that was inspired by the natural product structures.[8] As detailed in the accompanying article,[11] we extended the scope of an intermolecular 1,3,4-oxadiazole [4+2]/[3+2] reaction cascade beyond that which provides symmetrical 2:1 cycloadducts by implementing the reaction in an intramolecular fashion.[12] The reaction cascade is initiated by a [4+2] cycloaddition reaction of the 1,3,4-oxadiazole with a tethered dienophile that, for **3**, entailed the use of an electron-rich enol ether whose reactivity and regioselectivity were matched to react with the electron-deficient oxadiazole in an inverse electron demand Diels–Alder reaction (Figure 2). Loss of N_2 from the initial cycloadduct

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

provides a carbonyl ylide, which undergoes a subsequent 1,3-dipolar cycloaddition with a tethered indole.[13] For **3**, 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 dipolarophile (indole) complements the [3+2] cycloaddition regioselectivity that is set by the linking tether. The relative stereochemistry of the cascade cycloadduct is controlled by a combination of the dienophile geometry and an exclusive endo indole [3+2] cycloaddition dictated by the dipolarophile tether and sterically directed to the face opposite the newly formed fused lactam.[11-13] In the course of these studies and as key issues regarding the scope and stereochemical features of this new cycloaddition cascade were defined, it was implemented in the total synthesis of a series of related alkaloids, each bearing the characteristic pentacyclic carbon skeleton of vindoline (**3**), but of increasing complexity ultimately culminating with the total synthesis of **3** itself. Thus, full details of the total syntheses of both enantiomers of minovine (**4**),[14] 4-desacetoxy-6,7-dihydrovindorosine (**5**), 4-desacetoxyvindorosine (**6**), and vindorosine (**7**)[15] as well as the extension of the approach to provide N-methylaspidospermidine (**11**) are also provided herein. As a consequence of insights derived from these studies, an unusually concise synthesis of **3** was implemented enlisting the oxadiazole cycloaddition cascade to assemble the fully functionalized pentacyclic ring system with formation of four C–C bonds and three rings in a single step with direct introduction of all substituents and setting all six stereocenters within the central ring of vindoline including its three quaternary centers. Subsequent extensions of these studies to provide 6,7-dihydrovindoline (**8**), 4-desacetoxyvindoline (**9**), and 4-desacetoxy-6,7-dihydrovindoline (**10**) are also detailed herein.

Results and Discussion

Minovine and 4-desacetoxy-6,7-dihydrovindorosine

Minovine (**4**) is a naturally occurring alkaloid isolated from *Vinca minor* L.[16] and central to the biosynthetic pathway of many related alkaloids bearing the pentacyclic vincadifformine skeleton. It is much simpler in structure than vindoline and naturally occurring **4** was reported as possessing an $[\alpha]_D = 0$ in alcoholic solvents,[16] an unusual issue that was addressed with our preparation of optically active material. Prior reports of its synthesis[17] provided racemic material and no preceding studies have addressed the optical purity or definitive absolute configuration assignment of this alkaloid. 4-Desacetoxy-6,7-dihydrovindorosine (**5**) lacks the 6,7-double bond and C4-acetoxy group of vindorosine (**7**) as well as the additional C16 methoxy group of vindoline (**3**). Although it has not been isolated as a naturally occurring substance, it possesses nearly all the key stereochemical issues that a synthesis of vindoline incorporates.

The starting 2-amino-1,3,4-oxadiazole **16** for the synthesis of **4**–**7** was prepared from N-methyl tryptamine (**12**, Scheme 1). Treatment of **12** with carbonyldiimidazole afforded **13** (89%) that was converted to the oxadiazole precursor **15** (93%) by treatment with methyl oxalylhydrazide (**14**)[18] in the presence of HOAc. Cyclization of **15** to form the corresponding oxadiazole **16** was mediated by TsCl and Et_3N (83%).

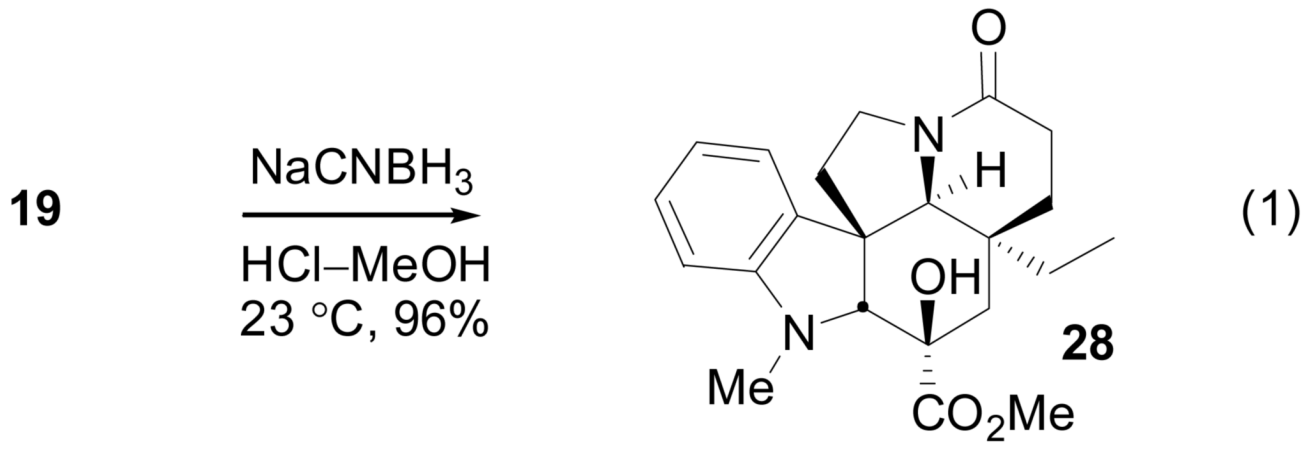
Coupling of **16** with 4-ethyl-4-pentenoic acid (**17**)[19] was effected by EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimidide hydrochloride) and DMAP to provide the substrate **18** (87%) for the key [4+2]/[3+2] cycloaddition cascade (Scheme 1). The tandem cycloaddition reaction proceeded in excellent yield (74%) upon warming a solution of **18** at 180 °C in *o*-dichlorobenzene for 24 h to provide **19** as a single detectable diastereomer possessing the characteristic alkaloid pentacyclic skeleton. The stereochemical assignments for **19** were first established by NMR through observation of diagnostic ^1H–^1H NMR NOEs (C5-Et/C14-H) and ultimately confirmed through X-ray analysis of synthetic **5**. The relative

stereochemistry of **19** is established in the [3+2] cycloaddition reaction and is derived from exclusive endo indole cycloaddition dictated by the dipolarophile tether and sterically directed to the face of the carbonyl ylide opposite the newly formed fused lactam.[11-13] Importantly, this sets the crucial relative stereochemistry key to accessing **3**–**11** enlisting the oxadiazole cycloaddition cascade.

Notably, as the dienophile becomes more highly substituted, the initiating [4+2] cycloaddition of the reaction cascade becomes progressively slower and this has been described in detail in the accompanying article.[11] However, one unanticipated consequence of this was observed while developing the approach to **4** and **5** that defined the importance of the acyl placement on the dienophile tether for the preparation of vindoline. That is, in all cases of a tethered indole, it participates in the reaction cascade as the dipolarophile and it has not been observed to serve as the dienophile initiating the reaction cascade. However, when we examined the substrate **24** bearing an unactivated and disubstituted dienophile with the N-acyl group placed in the dipolarophile tether, good conversions to the monocyclization product **25** were observed and only a trace of the tandem cycloaddition product was detected regardless of the reaction conditions (180–230 °C, 24–100 h), Scheme 2. Although this has not yet been examined in detail, it indicates that indole dienophile initiation of the reaction cascade is possible, and that in the presence of a tethered poor dipolarophile will likely result only in intercepted products derived from the Diels–Alder reaction. Notably, this contrasts the behavior of substrates in which the tethered dienophile olefin is unsubstituted and correspondingly much more reactive, where the cycloaddition cascade with substrates bearing the indole acyl tether (e.g., **26**) proceed uneventfully with the alkene, not the indole, participating in the initiating [4+2] cycloaddition. Most importantly, the observation with **24** clearly defined the N-acyl placement in the dienophile tether for the di- and trisubstituted dienophiles required of the alkaloids detailed herein.

A separation of the enantiomers of **19** ($\alpha = 1.19$) was carried out on a semipreparative Daicel ChiralCel OD column (2 × 25 cm, 10% *i*-PrOH–hexane, 10 mL/min flow rate) providing natural-(+)-**19** ($t_R = 31.7$ min) and *ent*-(−)-**19** ($t_R = 26.7$ min). The natural enantiomer series was initially assigned based on comparison with **5** which has been independently prepared in optically active form in prior studies[20] and was unambiguously established herein with an X-ray structure determination of the natural enantiomer of **20** bearing a heavy atom (S). Treatment of **19** with Lawesson's reagent[21] furnished this thiolactam **20** in 85% yield (Scheme 1, natural enantiomer shown). Desulfurization and opening of the oxido bridge was initially effected by reduction of **20** with Ra–Ni to provide **21** (90%) followed by diastereoselective reductive oxido bridge cleavage by Pt-catalyzed hydrogenation[13] of the intermediate iminium ion providing 4-desacetoxy-6,7-dihydrovindorosine (**5**, 73%).[20] Alternatively, *S*-methylation of the thiolactam **20** with Me_3OBF_4 followed by $NaBH_4$ reduction[22] in MeOH directly provided 4-desacetoxy-6,7-dihydrovindorosine [**5**, $[\alpha]_D^{24}$ +66 (*c* 0.10, MeOH) vs lit[20] $[\alpha]_D^{24}$ +30 (*c* 0.10, MeOH)] in superb yield (92%) in a single operation (Scheme 3). The disparity in the magnitude, but not sign, of the optical rotation of **5** raised concerns over the accuracy of our initial assignment of the absolute stereochemistry based on this comparison. However, a subsequent X-ray of (+)-**20** disclosed herein[23] enlisting sulfur as the heavy atom unambiguously confirmed the accuracy of this assignment. The even more direct approach of treating the lactam **19** with Meerwein's salt (Me_3OBF_4, CH_2Cl_2) and subsequent reduction ($NaBH_4$, MeOH) of the resulting methoxy iminium salt[24] also provided **5** but in lower conversions and in a reaction characterized by several additional byproducts. Finally, treatment of the lactam **19** 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 **28** in superb conversions (96%, eq. 1). Although not pursued for the preparation of **3**–**7**, this conversion permits the development of synthetic approaches to the Aspidosperma alkaloids in which the lactam carbonyl is maintained, as required of some natural products, or removed at a later stage

of the route as outlined in the following section. Significantly, the simple conversion of **19** to **28** demonstrates that reductive cleavage of the oxido bridge does not require prior lactam reduction. The relative stereochemistry in **5** was first established by observation of diagnostic $^1H–^1H$ NOEs between the C5 ethyl, C6, and C14 protons confirming the stereochemical course of the oxido bridge reductive ring opening reaction as well as that of the cycloaddition cascade and was confirmed with a single-crystal X-ray structure of **5**.[23] This clean control of all the relative stereochemistry about the central six-membered ring of **5** as well as the direct introduction of the C3 substituents and stereochemistry established the viability of the approach to vindoline. Treatment of **5** with the Burgess reagent[25] in CH_3CN first provided the sulfamate **22** (91%) which upon isolation and heating in toluene at 100 °C in the presence of NaH furnished minovine (**4**) and its isomer **23**. Although not investigated in detail, attempts to promote a direct single pot dehydration of **5** to provide **4** with the Burgess reagent were not successful. Since these reactions proceed at least in part by aziridinium formation via intramolecular sulfamate displacement favoring formation of **23**, no effort was made to alter or optimize the **4**:**23** ratio. It is plausible that **23**, whose exclusive formation from **5** might be possible, could prove useful in the synthesis of vindoline through syn dihydroxylation of the C3–C4 double bond and such intermediates have been utilized in past efforts.[9c] However, such an approach fails to capitalize on the intrinsic C3 substitution and stereochemistry introduced in the oxadiazole cycloaddition cascade and, as such, was not pursued.



(1)

Naturally occurring minovine (**4**) was reported with an $[\alpha]_D = 0$ in alcoholic solvents.[16] This raised the question of whether the rotation of **4** was simply 0 or whether natural minovine might suffer a facile racemization that could be envisioned to occur by retro [4+2] cycloaddition providing an intermediate lacking any stereocenters followed by a diastereoselective, but not enantioselective, [4+2] cycloaddition. With optically active minovine in hand, we found that it exhibited a remarkable solvent dependent, but concentration independent, range of optical rotations: natural **4** $[\alpha]_D^{23}$ −17 (*c* 0.35, $CHCl_3$), +16 (*c* 0.40, MeOH), and 0 ±3 (*c* 0.28, EtOH). Moreover, the enantiomeric integrity of **4** was maintained not only upon prolonged storage at 25 °C, but also upon deliberate attempts to promote racemization via a reversible Diels–Alder reaction. Thus, warming **4** in MeOH (80 °C, 24–48 h), toluene (120 °C, 21 h), or DMF (80–160 °C, 20 h) led to no evidence of racemization, albeit with variable amounts of decomposition. The potential racemization was easily monitored by chiral phase HPLC where the two enantiomers of **4** were readily separable (t_R = 10.0 min (natural **4**) and 8.29 min (*ent*-**4**), ChiralCel OD 0.46 × 25 cm column, 0.5% *i*-PrOH–hexane, 1 mL/min flow rate, α = 1.21). Thus, naturally occurring minovine exhibits an unusual optical rotation, whose sign is

dependent on the choice of solvent. In EtOH, its value is 0 as reported,[16] but this is not necessarily because it is racemic.

Although we established this unusual behavior of optically active minovine, we have not yet been provided the opportunity to compare our synthetic material with an authentic sample of the natural product. Consequently, our assignment of the "natural" and "unnatural" enantiomer series in the discussion above rests with the correlation made by Ziegler[17b] enlisting an ORD comparison of natural minovine with (−)-vincadifformine. It is possible that both enantiomers of **4**, like those of vincadifformine,[26] may be found to occur naturally. Thus, while the absolute configuration of our synthetic material is unambiguously established with the X-ray structures, the designation of "natural" minovine in the discussion above isolated from *Vinca minor*[16] is based on the Ziegler assignment[17b] and is further supported by the observation that the same plant source also produces (−)-vincadifformine[16d] ($[\alpha]_D$ −600 in EtOH) of this same absolute configuration (Figure 3).[26]

N-Methylaspidospermidine

The unfunctionalized pentacyclic skeleton of **3**, aspidospermidine, has been the focus of a beautiful series of racemic and enantioselective total syntheses that have characterized efforts directed at this class of alkaloids.[27,28] Remarkably, it possesses a naturally occurring absolute configuration opposite that found in vindoline and the vinca alkaloids. A closely related minor alkaloid also identified in this class is N-methylaspidospermidine (**11**) which, unlike aspidospermidine itself, has not been prepared by total synthesis and whose absolute configuration was assigned by correlation of its ORD spectrum with that of (+)-aspidospermidine.[29b,30] It has been isolated not only from *Evatamia peduncularis*,[29c] *Vallesia dichotoma*,[29a] and *Aspidosperma quebracho blanco*,[29d] but also *Vinca minor* L.[29b] apparently with the same absolute configuration ($[\alpha]_D$24 +24 (*c* 1.25, $CHCl_3$)[29b] and +21 ($CHCl_3$)[29a]). Thus, following the completion of the total synthesis of vindoline detailed in a following section, we elected to further highlight the applicability of 1,3,4-oxadiazole cycloaddition cascade for the synthesis of such simplified Aspidosperma alkaloids with N-methylaspidospermidine (**11**) where, to our knowledge, the efforts would not only constitute the first total synthesis,[29c] but also serve to unambiguously confirm its absolute configuration. Moreover, it represented an opportunity to further explore and highlight the optional order of lactam carbonyl reduction/oxido bridge opening following the cycloaddition cascade.

Thus, treatment of the resolved cycloaddition product **19** with HCl (3 equiv) in the presence of $NaCNBH_3$ (6 equiv, MeOH, 23 °C, 1.5 h) cleanly provided **28** in superb conversion (96%) (Scheme 4, natural enantiomer shown). Subsequent treatment of **28** with $LiAlH_4$ (10 equiv, THF, reflux, 15 h, 99%) provided **29** derived from lactam reduction to the tertiary amine and concurrent ester reduction to the corresponding alcohol. Initial, alternative attempts to convert **19** directly to **29** in a single step with $LiAlH_4$ (15 equiv, THF, reflux, 16 h) provided **29** in lower conversion (31%) and predominantly afforded products derived from partial reduction. Given that the two-step reduction sequence was so efficient (95–96%), this single step conversion was not examined in further detail, but likely could be optimized to achieve a more satisfactory conversion. Cleavage of diol **29** with $NaIO_4$ (6 equiv, acetone–H_2O, 25 °C, 3 h, 93%) provided the sensitive ketone **30** in excellent conversion. Storage of **30** (0 °C, 3 d) or its subjection to a short series of classical methods for reductive removal of a ketone led to significant competitive decomposition. Consequently and without storage, **30** was cleanly reduced with $NaBH_4$ (10 equiv, EtOH, 25 °C, 1 h, 99%) in a reaction that provides the stable axial alcohol **31** as a single diastereomer derived from equatorial hydride delivery (C2-H; d, *J* = 2.5 Hz). Subsequent conversion of **31** to the methyl dithiocarbonate **32** (2.5 equiv of LiHMDS, 20 equiv of CS_2, THF, −10 °C, 4 h followed by 10 equiv MeI, 25 °C, 12 h, 77%) and its Barton–McCombie deoxygenation (Bu_3SnH, cat. AIBN, toluene, reflux, 1 h, 96%)

cleanly provided (+)- and *ent*-(−)-N-methylaspidospermidine (**11**) for which the naturally occurring enantiomer [lit[29b] $[\alpha]_D^{24}$ +24 (*c* 1.25, $CHCl_3$)] was established to possess the absolute configuration shown in Scheme 4 [synthetic **11** depicted: $[\alpha]_D^{25}$ +26 (*c* 0.76, $CHCl_3$)].

Notably, N-methylaspidospermidine and such simplified Aspidosperma alkaloids lack substitution at the C3 position that the 1,3,4-oxadiazole cycloaddition cascade so purposely introduces. We initially imagined that this functionality could be usefully adjusted by enlisting a 1,3,4-oxadiazole bearing a nitrile substituent which, upon reductive oxido bridge opening, would release a cyanohydrin that in turn would collapse to a ketone. This would not only serve to extend the cycloaddition scope by permitting the direct introduction of alternative useful functionality (a ketone) following oxido bridge cleavage, but it would also allow direct access to the Aspidosperma alkaloids by subsequent removal of the ketone. Consequently, we examined the cycloaddition reactions of the 1,3,4-oxadiazoles **33** and **37** which bear a C5 nitrile versus methyl ester (Scheme 5). The reaction of **33** bearing the unsubstituted and unactivated terminal alkene cleanly provided a single diastereomer of the cascade cycloadduct **34** in good conversions (*o*-$Cl_2C_6H_4$, 180 °C, 75%)[11] requiring the short reaction times (3 h) characteristic of such substrates. Cleavage of the oxido bridge mediated by acid catalysis in the presence or absence of $NaCNBH_3$ provided the stable cyanohydrin **35**. Upon standing, **35** was found to revert back to **34**, whereas base treatment of **35** provided the sensitive ketone **36**. Thus, although the intermediate N-acyl iminium ion was not reductively trapped under the reaction conditions, the tactical release of ketone upon oxido bridge cleavage was established. Efforts to extend these observations to substrates that permit access to the Aspidosperma alkaloids have been disappointing to date, but for unexpected reasons. In contrast to **33** which participates in the cycloaddition cascade uneventfully, **37** bearing the tethered disubstituted terminal alkene with the additional ethyl substituent proved problematic. The best conversions to date (15–26%) fall far short of those observed with **33** (or **18**) and appear to stem from a sensitivity of the cycloadduct **38** itself to the reaction conditions for the time required for complete reaction (TIPB, 230 °C, 12 h or *o*-$Cl_2C_6H_4$, 180 °C, 24 h).[11] Although this has not been carefully examined, such problems have not been encountered with **18** or other 1,3,4-oxadiazoles bearing a C5 methyl ester. Nonetheless and with samples of **38** in hand, its conversion to ketone **40** by acid-catalyzed (5 equiv of HCl) reductive oxido bridge cleavage (6 equiv of $NaCNBH_3$, MeOH, 25 °C, 1 h) proved viable illustrating the potential of such an approach.

4-Desacetoxyvindorosine

In addition to provisions to incorporate the C16 methoxy substituent unique to **3**, introduction of the C6–C7 double bond and the C4 acetoxy substituent would be required to implement the approach for vindoline itself. The latter was anticipated to arise from an appropriate substituent on the tethered dienophile,[11] whereas the former would require its introduction following the cycloaddition cascade. Consequently, numerous approaches to the timing and method for the introduction of the C6–C7 double bond were examined. Whereas many of these are detailed in the following sections, the approach that was employed enlisted an α-hydroxylation of the cycloadduct lactam. Following lactam carbonyl excision and reductive oxido bridge cleavage, a late stage regioselective secondary alcohol elimination was anticipated to provide the $\Delta^{6,7}$-alkene introduction. The latter elimination reaction was well precedented having been used in the pioneering approach of Kuehne[31] and later by Fukuyama,[10c] albeit on early stage synthetic intermediates rather than the penultimate intermediate. In our hands, both these reactions required considerable optimization over a period of years. The challenges associated with the α-hydroxylation reaction were addressed while pursuing vindorosine and vindoline and are accordingly discussed in the following sections. The unanticipated challenges associated with the final introduction of the $\Delta^{6,7}$-alkene via the secondary alcohol elimination were addressed with **46**, providing a total synthesis of 4-desacetoxyvindorosine (**6**, aka 2,3-dihydro-3-hydroxy-

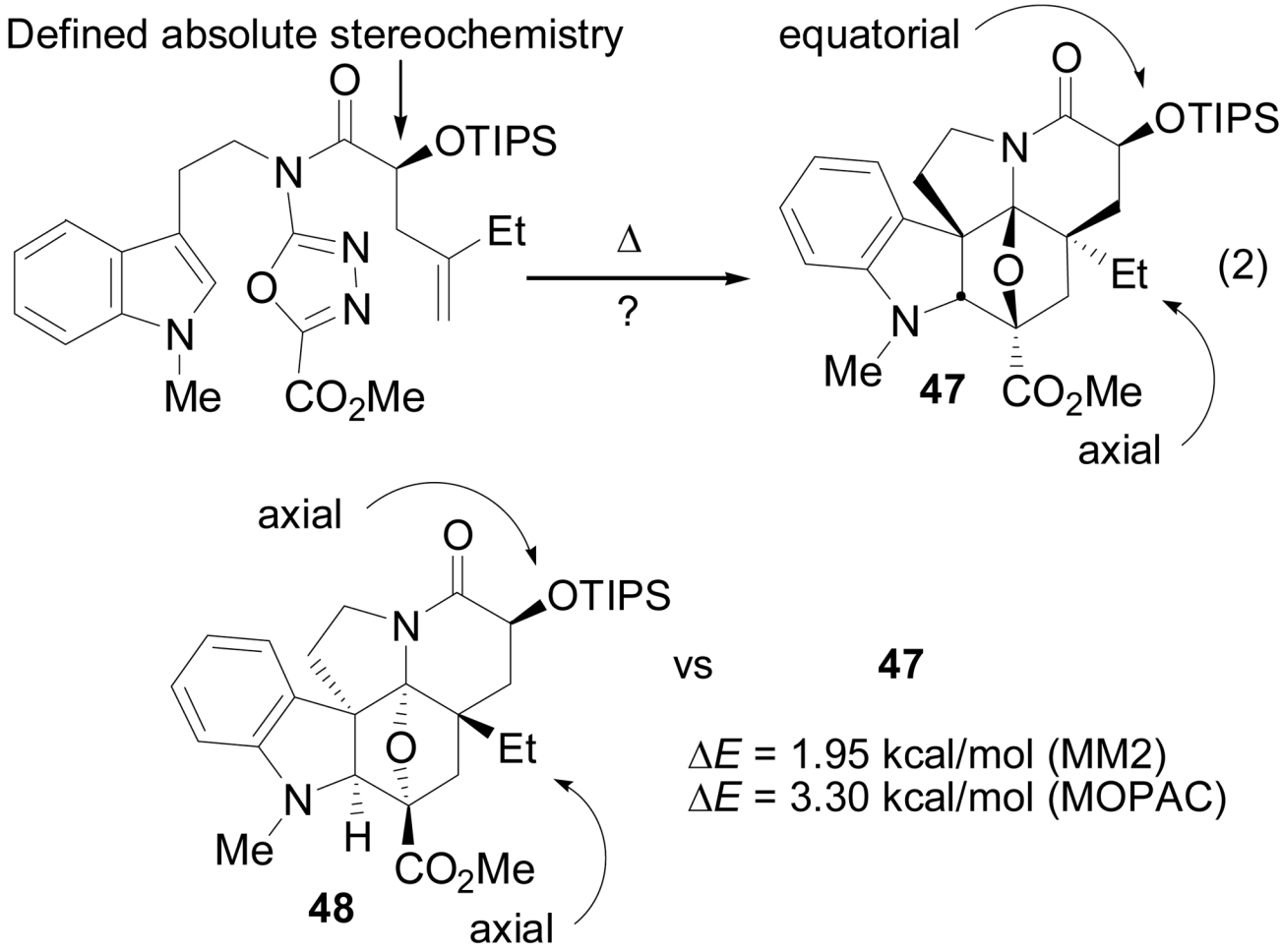
N-methyltabersonine),[32] a key late stage biosynthetic intermediate enroute to vindorosine requiring only the final C4-hydroxylation and subsequent *O*-acylation. Despite its natural origin as well as its structural and biosynthetic relationship with vindorosine (**7**), we are not aware of a total synthesis of this alkaloid.[33]

Thus, as we faced unexpected difficulties in conducting the final elimination reaction required for both vindorosine and vindoline, we elected to examine this reaction in detail with the more readily accessible substrate **46**. α-Hydroxylation of **19** under conditions optimized for vindorosine and vindoline (2 equiv of NaHMDS, 4 equiv of TMSOOTMS, −45 °C, 1 h, 51%) followed by silyl ether protection of the isolated alcohol **41** (2 equiv of TIPSOTf, 3 equiv of Et_3N, 25 °C, 0.5 h, 94%) provided **42** (Scheme 6, only natural enantiomer shown). Like the observations first made in the following studies, this provided the equatorial C7 alcohol as the predominant, perhaps exclusive, product. Although C7-H of **41** was obscured by other signals, the stereochemistry resulting from the α-hydroxylation reaction was clear upon ^1H NMR analysis of **42** (C7-H; dd, J = 11.7, 5.8 Hz) and unambiguously established by X-ray of **43**.[23] This latter X-ray conducted on the natural enantiomer with a derivative containing a heavy atom (S) was also of a quality that supported, but did not unambiguously establish, the absolute configuration assignment for **6**. Thiolactam formation enlisting Lawesson's reagent[21] (90%), reductive desulfurization of **43** with Ra–Ni (90%), diastereoselective reductive cleavage of the oxido bridge in **44** upon catalytic hydrogenation (H_2, PtO_2, 96%),[13] and silyl ether deprotection (Bu_4NF, 91%) provided **46**. Subsequent secondary alcohol activation and elimination (2 equiv of Ph_3P, 3 equiv of DEAD, THF, 25 °C, 24 h, 78%) cleanly provided **6** identical in all respects with properties reported for naturally-derived material [lit[33] $[\alpha]_D$ +48 (*c* 0.7, MeOH); synthetic $[\alpha]_D$[23] +49 (*c* 0.3, MeOH)].

Initial efforts to promote the C7 alcohol elimination included an exhaustive study of the procedures detailed by Kuehne[31] (Ph_3P–CCl_4, Et_3N) and Fukuyama[10c] (Ph_3P–CCl_4) on simpler substrates. In general, the reaction was not easily implemented and proved sensitive to contaminant moisture leading to regeneration of the starting alcohol potentially from an intermediate aziridinium ion, and intolerant of excess reagent that results in competitive in situ chloride displacement or addition to the aziridinium ion (Scheme 7). As first alluded to by Kuehne,[31] the chloride addition to a putative aziridinium ion is potentially reversible, and can provide two regioisomeric products whose appearance and ratio is condition and temperature dependent. Although improvements in the reaction were implemented by ensuring anhydrous reaction conditions (no water nucleophile to regenerate starting material), by limiting the reagent stoichiometry (≤ 1.3 equiv Ph_3P–CCl_4, limiting the competitive chloride nucleophile), by systematic alterations in the solvents (CH_2Cl_2, $ClCH_2CH_2Cl$ > CH_3CN > THF), with adjustments to the reaction temperature (70–80 °C > 25 °C), and with inclusion of a base (py > Et_3N, *i*-Pr_2NEt > collidine > DABCO) to promote in situ elimination, the conversions remained modest (50–55%), challenging to reproduce, and still plagued by generation of additional byproducts. Moreover, the conditions (1.3 equiv of Ph_3P, 1.3 equiv of CCl_4, 2.25 equiv of py, CH_3CN, 70 °C, 2 h, 56% with 28% of a major byproduct; 1.3 equiv of Ph_3P, 10 equiv CCl_4, 5 equiv of py, $ClCH_2CH_2Cl$, 80 °C, 3 h, 51% with 23% of a major byproduct) did not immediately generalize to the more highly functionalized substrates required for vindoline or vindorosine where the conversions, albeit on smaller scales, were typically lower. Nonetheless, the detailed study revealed the key features limiting the reaction. A more effective approach to this elimination would enlist reagents that do not liberate a nucleophile under the reaction conditions and, optimally, would stoichiometrically generate the base required to promote the elimination or fragment the intermediate aziridinium ion. These requirements are met by the Mitsunobu reagent[34] Ph_3P–DEAD which first activates the secondary alcohol for displacement, releases the innoculus byproduct Ph_3PO upon elimination or transannular aziridinium ion formation, and even supplies (generates) the base (EtO_2CN^-–$NHCO_2Et$) for the reaction. As such, the conversion of **46** to **6** occurs in high yield under a wide range of mild

conditions even in the presence of excess reagent and in the absence of added base when conducted enlisting Ph_3P–DEAD.

One final feature that we examined with **6**, that impacts the potential of developing an asymmetric synthesis, was the prospect of incorporating the C7-hydroxy group into the dienophile tether prior to the implementation of the cycloaddition cascade (eq. 2). Not only would this shorten the post cycloaddition synthetic sequence by two steps and avoid the technically challenging lactam α-hydroxylation providing an exquisitely short synthesis, but the use of a chiral center in the linking tether might be anticipated to define the absolute as well as relative stereochemical outcome of the cycloaddition cascade. Simple ground state modeling of the potential cycloaddition products, disregarding the oxadiazole endo/exo diastereoselection which is lost upon elimination of N_2, suggested that incorporation of a substituent α to the carbonyl in the dienophile tether could be expected to occupy an equatorial versus axial position on the tethered six-membered ring adopting a chair-like conformation in the [4+2] cycloaddition transition state. Adoption of the alternative axial orientation appeared to be especially destabilized since it entailed a developing OR/Et 1,3-diaxial interaction (ΔE = 1.9–3.3 kcal/mol). Following an initial trial examination of a substrate bearing an α-silyloxy substituent in the dienophile tether which produced at least two cycloadducts, we elected to more carefully examine the effect of a dienophile tether substituent with **49**, **52**, and **55**, bearing an α-methyl substituent.



The first such substrate examined, **49**, bears the amide carbonyl in the dienophile tether and was prepared by N-acylation (EDCI, DMAP, CH_2Cl_2, 25 °C, 16 h, 81%) of **16** with (*S*)-2-methyl-4-ethyl-4-pentenoic acid.[35] Warming **49** in either *o*-$Cl_2C_6H_4$ (180 °C, 24 h, 5 mM) or TIPB (230 °C, 24 h, 5 mM) provided a disappointing mixture of **51** (53–44%) and **50** (29–32%) in which it was the minor product **50** that possessed the desired relative and absolute configuration (Scheme 8). The stereochemical assignment for **50** was established by observation of diagnostic NOEs between C7-H/C5-Et and C5-Et/C14-H, and arises from a tethered chair-like transition state with the methyl substituent adopting an equatorial position in the fused six-membered ring (C5-Et/C7-Me are trans in **50**). The major product **51**, whose structure was unambiguously established by X-ray,[23] possesses the correct relative stereochemistry for the alkaloids, but the opposite absolute stereochemistry required for vindoline (at C2, C3, C5, C12) and the C5-Et/C7-Me substituents are unexpectedly cis.[36] Thus, the major product arises from a tethered boat-like transition state for the fused six-membered ring. This could be used to install the correct absolute as well as relative stereochemistry simply by utilizing the enantiomer of **49**, but the 1.3–1.6:1 ratio of **51** to **50** indicates that the desired substituent-induced control of the absolute configuration would be modest. Thus, the facial selectivity induced by the linking chain substituent in substrates like **49** is modest resulting from competitive transition states of the initiating [4+2] cycloaddition reaction in which the dienophile linking chain adopts both a chair (minor) or boat-like (major) conformation (Figure 4). Notably, the relative stereochemistry that is set in the subsequent dipolar cycloaddition is unaffected by the tethered dienophile substitution being directed to the face opposite the newly formed fused lactam and confined to endo addition by the dipolarophile tether. As a consequence of these observations, we also examined the substrates **52** and **55** in which the linking carbonyl was placed in the dipolarophile, not dienophile, tether (Scheme 8).[37] Expectations were that this would now favor the adoption of a chair-like conformation for the dienophile tether in the [4+2] cycloaddition transition state by removing an imbedded sp^2 center (Figure 4). Substrate **52**, bearing an unsubstituted terminal alkene as the dienophile provided a 1.7:1 mixture of **53** and **54**[23] now favoring the expected product **53** in which the dienophile linking chain adopts the chair-like conformation with an equatorial methyl substituent that in turn sets the remaining relative and absolute configuration. Beautifully, the X-ray structures of **51**[23] and **54**[23] reflect these interpretations with the final lactam of **51** adopting a boat-like conformation with the C5 ethyl group occupying the axial “flagpole” position and the cis C7 methyl group adopting a pseudo equatorial position, whereas the saturated piperidine ring of **54** adopts a chair conformation with the C7 methyl group adopting an axial position cis to the axial C5 hydrogen substituent. Aside from this modest diastereoselection with substrate **52** bearing a C5-H (vs Et) substituent, the substrate **55** incorporating both the dipolarophile amide tether and the less reactive disubstituted dienophile required of the alkaloids expectedly provided principally the product of an indole initiated [4+2] cycloaddition (**57**, 48–72%) and a small amount of **56** (7–11%) along with two other more minor unidentified products. Nonetheless, **56** possessed the requisite relative and absolute configuration required of vindoline exhibiting diagnostic NOEs between C7-H/C5-Et and C5-Et/C14-H and confirming the rationale for the stereochemical observations.

Vindorosine

Vindorosine (**7**)[38] is among the most complex, highly functionalized and stereochemically rich natural products within the family of alkaloids isolated from the Madagascan periwinkle (*Catharanthus roseus* (L.) G. Don). It is identical in structure to vindoline with the exception that it lacks the C16 methoxy substituent. As a consequence, it has been the subject of a series of beautiful and historically important total syntheses.[39] In conjunction the efforts on vindoline, we also developed an unusually concise total synthesis of (−)- and *ent*-(+)-vindorosine complementary to these past efforts.[15] This focus on vindorosine arose principally as a result of the greater accessibility and reduced electrophilic character of the precursor indole

that facilitated a detailed study of the key cycloaddition reaction. The expectation being that the tethered dienophile would now bear substitution that would permit the introduction of the C4 acetoxy group; the remaining functionality necessary to directly access vindoline through the [4+2]/[3+2] cycloaddition cascade. Thus, coupling of the 1,3,4-oxadiazole **16** with either (*Z*)- or (*E*)-5-benzyloxy-4-ethyl-4-pentenoic acid (**58**) provided the key cycloaddition precursors (*Z*)- or (*E*)-**59** bearing isomeric trisubstituted electron-rich enol ethers as the tethered dienophiles (Scheme 9). As detailed in the accompanying article, trisubstitution of the dienophile typically precludes [4+2] cycloaddition initiation of the reaction cascade. The exception to this generalization is the use of trisubstituted olefins bearing an electron-donating substituent to activate the tethered dienophile for participation in an inverse electron demand Diels–Alder reaction with the electron-deficient 1,3,4-oxadiazole. Thus, the electron-rich dienophiles of (*Z*)- and (*E*)-**59** were ideally suited for initiation of the cycloaddition cascade enhancing the intrinsic reactivity of the dienophile, reinforcing the [4+2] cycloaddition regioselectivity dictated by the dienophile tether, and directly introducing the C4 alkoxy substituent. The distinction in the two substrates being that (*Z*)-**59** permits the direct introduction of the naturally occurring C4 acetate β-stereochemistry, whereas (*E*)-**59** provides the C4 isomer requiring a subsequent inversion of configuration at this center. Contrary to expectations, the substrate (*Z*)-**59**, which directly provides the preferred cycloadduct **60** for use in the synthesis of **7**, proved to be the more difficult to implement. As such, these two cycloaddition cascades were examined in detail. Cyclization of (*E*)-**59** proceeded especially effectively providing a single detectable diastereomer **61** in superb conversions (86%, *o*-$Cl_2C_6H_4$, 24 h), Scheme 9. In an early survey of this reaction, the conversions were more modest (30–40%) when conducted at conventional reaction concentrations (0.2–0.1 M), but increased significantly when the concentration was reduced to 0.005 M. This initial observation remained unexplored for a considerable period of time as the interest in promoting the tandem cycloaddition cascade of the preferred substrate (*Z*)-**59** under these conditions was pursued. However, upon revisiting this impact of the reaction concentration, yields of the cycloadduct **61** from (*E*)-**59** were found to exceed 95% (TIPB, 230 °C, 18 h, Table 1) upon further dilution. By contrast, the tandem cycloaddition of (*Z*)-**59** proved more challenging to implement. After considerable exploration as detailed below, (*Z*)-**59** was found to provide the desired cycloadduct **60** in good yield (78%) as a single detectable diastereomer when warmed in triisopropylbenzene (TIPB, 230 °C, 60 h). Initial attempts to promote the cycloaddition of (*Z*)-**59** provided **60** in modest conversion (≤30–40% at ≥5 mM) when conducted under the conditions initially adopted for (*E*)-**59**. However, further dilution of the reaction led to improved conversions ultimately providing **60** in yields as high as 78%. As a result, this impact of the reaction concentration on the cascade cycloaddition of both (*Z*)- and (*E*)-**59** was retrospectively and systematically examined (Table 1). Both were found to exhibit a significant dependence on the reaction concentration with that of (*Z*)-**59** being much more pronounced suggesting that a competitive bimolecular reaction may compete with the intramolecular cycloaddition cascade at the higher reaction concentrations.

More significantly, we observed that the [4+2] cycloaddition of (*Z*)-**59** is now the fast step in the reaction cascade and that the subsequent [3+2] cycloaddition is the slow step, a reversal of what is observed with (*E*)-**59** and other typical substrates.[11] The net consequence of this observation is that longer reaction times and/or more vigorous reaction conditions, in conjunction with the use of dilute reaction concentrations, led to substantial improvements in the conversion of (*Z*)-**59** to **60**. Thus, premature workup of the cycloaddition reaction resulting from shorter reaction times or milder reaction conditions provided products (**62**, See Supporting Information) derived from a quench of the intermediate 1,3-dipole or the corresponding cyclobutene epoxide. Notably, the analogous cycloaddition cascade of (*E*)-**59** not only proceeds under milder conditions (180 °C, 24 h), but also with little or no detection of products derived from quench of the intermediate 1,3-dipole if the reaction is prematurely stopped. Although such observations were first misinterpreted to represent an instability of the

intermediate 1,3-dipole derived from (*Z*)-**59** under the reaction conditions resulting in a search for milder (not more vigorous) conditions, we ultimately found that simply extending the reaction times and raising the reaction temperatures increased the conversions to **60** and the intermediate-derived byproducts diminished or disappeared altogether. The origin of this distinction in the slow step of the cycloaddition cascade of (*Z*)- versus (*E*)-**59** was not clear. In fact, the 1,3-dipolar cycloaddition transition state for (*E*)-**59** would appear to embody the serious steric interactions disfavoring the observed indole endo approach on the α-face of the 1,3-dipole, yet it progresses with a greater facility than that of (*Z*)-**59** (Scheme 9). It is possible that the preferred stereochemistry of the corresponding cyclobutene epoxides 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. However, in examining the relative transition states for the 1,3-dipolar cycloadditions, it is also possible that (*Z*)-**59** may suffer a destabilizing electrostatic interaction of its central oxygen with the OBn substituent that decelerates the reaction or that the OBn substituent of (*E*)-**59** stabilizes its transition state (transition state anomeric effect). We are unaware of any studies that might have previously distinguished such effects and their magnitude is surprising.

To probe the origin of this effect, (*E*)- and (*Z*)-**63** bearing a terminal methyl substituent on the tethered dienophile in place of the benzyloxy substituent were examined (Scheme 10). The expectation being that if the electronic nature of the benzyloxy substituent was responsible for the differences observed in the slow step of the cycloaddition cascade with (*Z*)-**59** ([3+2] cycloaddition) versus (*E*)-**59** ([4+2] cycloaddition), these differences would disappear in the comparisons of (*Z*)- and (*E*)-**63**. Thus, the methyl versus benzyloxy substituents would be expected to mirror or perhaps enhance the steric effects on the [3+2] cycloaddition of the reaction cascade, but remove the electronic effects influencing the relative rate of the [3+2] cycloaddition. Without optimization and much more consistent with expectations, both (*Z*)- and (*E*)-**63** participated effectively in the cycloaddition cascade and did so at essentially identical rates without detection of products derived from the intermediate 1,3-dipole ([3+2] faster than [4+2]), Scheme 10. In fact, when the reaction was followed by ^{1}H NMR in *o*-$Cl_2C_6D_4$, (*Z*)-**63** participated in the cycloaddition cascade at what might be a slightly greater rate and with what appears to be cleaner conversions to the expected product consistent with its less sterically encumbered [3+2] cycloaddition transition state. Diagnostic NOEs between NMe/C4-H, C4-H/C5-H, and C5-H/C14-H observed with **64** derived from (*Z*)-**63** and between NMe/C4-Me, C4-Me/C5-H, and C5-H/C14-H for **65** derived from (*E*)-**63** confirmed the stereochemical assignments of the cycloadducts.

These observations established that it is the electronic character of the benzyloxy substituent of (*Z*)-**59** that is decelerating the typically fast 1,3-dipolar cycloaddition. We attribute this deceleration of the 1,3-dipolar cycloaddition to a destabilizing electrostatic interaction of the benzyloxy substituent with the central oxygen of the carbonyl ylide present only in the [3+2] cycloaddition transition state for (*Z*)-**59** that is absent with (*E*)-**59** (Scheme 9). An additional, more provocative, explanation rests with the preferred stereochemistry of the potential intermediate cyclobutene epoxides. Reversible ring closure to the cyclobutene epoxides by the intermediate 1,3-dipoles derived from (*Z*)- and (*E*)-**59**, which could serve as a reservoir for the reactive carbonyl ylides, may well possess preferred epoxide stereochemistries that influence the ease of the tethered 1,3-dipolar cycloaddition. Thus, the cyclobutene epoxide derived from (*E*)-**59** might be expected to possess the β-stereochemistry indicated in Figure 5 placing the epoxide on the cyclobutane face opposite the ethyl and benzyloxy substituents and opposite the incoming indole dipolarophile. Not only does this allow direct unfettered access of the indole dipolarophile to the endo face of the 1,3-dipole as it is reversibly generated, but it also represents a strained trans-fused 6,4-ring system destabilizing the cyclobutene epoxide. In contrast, the most stable cyclobutene epoxide derived from (*Z*)-**59** places the epoxide on the α-face, trans to the electronegative benzyloxy substituent within a more stable cis-fused 6,4-

ring system. This not only places the epoxide on the same face as the approaching indole dipolarophile potentially blocking its access, but it also represents a more stable cyclobutene epoxide. Either, or perhaps both features, may contribute to the slower [3+2] cycloaddition observed with (*Z*)-**59**.

The enantiomers of cycloadduct **60** proved easily separable by chiral phase chromatography (ChiralCel OD column, 2 × 25 cm, 20% *i*-PrOH–hexane, 10 mL/min, t_R = 15.2 (natural) and 21.3 min, α = 1.40) providing access to either enantiomer on a preparatively useful scale (150 mg/injection). α-Hydroxylation of **60** was achieved by treatment of the lactam enolate (generated with LDA) with TMSO–OTMS[40] and was followed by a direct quench with triisopropylsilyltriflate (TIPSOTf) providing silyl ether **69** (60%), Scheme 11 (only natural enantiomer shown). The α-hydroxylation proceeded in a stereoselective manner providing **69** as a single diastereomer bearing an equatorial substituent (C7-H; dd, *J* = 12.3, 6.2 Hz) resulting from approach of the electrophile from the least hindered convex face of the enolate. Interestingly, this reaction performed best (≥60%) when the TMSO–OTMS was premixed with the lactam **60** and subsequently treated with base (NaHMDS or LDA) at low temperature (−78 °C), and provided lower conversions (ca. 20%) if the lactam enolate was first generated and then treated with the reagent. Typically, LDA provided the highest conversions if the substrate contained a C4 substituent (e.g. **60, 80** and **81**), but was generally less satisfactory than NaHMDS if the substrate did not contain a C4 substituent (e.g. **19** or **109**). In these latter instances, amidation of the C3 methyl ester was observed with the less hindered amide base (LDA) under the conditions used to drive the reaction to completion. Several alternative and more conventional α-hydroxylation procedures were also examined including the use of the Davis oxaziridines (LDA or NaHMDS, (+)- or (−)-CSO, 30–50%)[41] and its many modifications ((+)-Cl_2CSO, DPO),[42,43] O_2,[44] PhNO[45] or MoOPH,[46] and each proved less satisfactory, providing substantial amounts of recovered lactam or, if forced, complete consumption of starting material without improvements in the conversions.

The amide **69** was converted to thioamide **70** (93%) with Lawesson's reagent.[21] Reduction of the thioamide with Ra–Ni occurred cleanly in 2 h, but the reaction was allowed to proceed longer (16 h) leading to subsequent cleavage of the benzyl ether providing the alcohol **71** (80%) directly in a single step. Acetylation of secondary alcohol **71** with acetic anhydride (97%) followed by a diastereoselective reductive oxido bridge opening of **72** (93%, H_2, PtO_2),[13] and subsequent deprotection of the TIPS ether **73** with Bu_4NF afforded diol **74** (99%). A final regioselective elimination of the secondary alcohol **74** using the newly developed conditions enlisting Ph_3P–DEAD (THF, 23 °C, 24 h, 74%) cleanly provided (−)- and *ent*-(+)-vindorosine (**7**).

It is possible that an earlier stage introduction of the $\Delta^{6,7}$-alkene that would avoid the late stage C7 alcohol elimination could be implemented in a synthesis of vindorosine and this would simply entail reactions of the lactam enolate derived from **60** with alternative electrophiles more commonly enlisted to provide an unsaturated lactam. Such reactions proceed more effectively than the α-hydroxylation of **60** and are easily transformed to the unsaturated lactam (Scheme 12). However, difficulties arise in the order and manner in which the subsequent transformations are conducted. Preliminary attempts at lactam or thiolactam reduction to the tertiary amine without reduction or migration of the $\Delta^{6,7}$-alkene did not appear straightforward, oxido bridge cleavage in the presence of the unmodified unsaturated lactam resulted in a subsequent conjugate addition of the liberated C3 tertiary alcohol to provide an extraordinarily stable ether, and the requisite C4 benzyl ether deprotection and reductive oxido bridge cleavage were relegated to methods (not a combined Ra–Ni reduction) that would not competitively reduce the $\Delta^{6,7}$-alkene. It was these observations and considerations that led to our commitment to the approach detailed in Scheme 11 requiring development of satisfactory solutions to the α-hydroxylation of **60** as well as the late stage regioselective C7 alcohol elimination.

Finally, we also examined a range of functionalized tethered dienophiles that potentially could have provided an alternative, albeit less direct, introduction of the C4 alkoxy group (Figure 6). Notably, none of these performed as effectively as (*Z*)- or (*E*)-**59** and were not pursued beyond an initial examination.

Vindoline

The preceding studies set the stage for implementation of a remarkably concise 11-step total synthesis of vindoline (**3**). Treatment of N-methyl-6-methoxytryptamine (**75**)[47] with carbonyldiimidazole (CDI, 90%) followed by subsequent reaction of **76** with methyl oxalylhydrazide[18] (**14**) furnished **77** (79%), Scheme 13. Closure of **77** to the 1,3,4-oxadiazole **78** (1.0 equiv of TsCl, 2.5 equiv of Et_3N, CH_2Cl_2, 23 °C, 81%) and subsequent N-acylation with isomerically pure (*Z*)- or (*E*)-**58** provided the key cycloaddition substrates (*Z*)-**79** (96%) and (*E*)-**79** (92%) now bearing the tethered 6-methoxyindole dipolarophile and the stereochemically defined electron-rich dienophiles. Both (*Z*)- and (*E*)-**79** underwent the key tandem [4+2]/[3+2] cycloaddition cascade to give the pentacyclic products **80** (53%) and **81** (>95%), respectively, as single diastereomers whose structures were assigned initially based on their ^1H NMR spectroscopic properties and later unambiguously established with single-crystal X-ray structures.[23] Consistent with the concurrent observations made in the approach to vindorosine detailed in the preceding section, the reaction of (*E*)-**79** proceeds more rapidly than (*Z*)-**79**, the slow step for the cascade cycloaddition of the former is the initiating Diels–Alder reaction whereas that of the latter is the [3+2] cycloaddition, and both exhibit a significant concentration effect (Table 2) that is most pronounced with (*Z*)-**79**.

Although unanticipated, the enantiomers of **80** could be easily separated on a Chiralcel OD column (30% *i*-PrOH–hexanes, 2 × 25 cm) with a remarkable efficiency (α = 1.70, t_R = 15.1 (natural) and 25.6 min, 10 mL/min), providing access to either enantiomer on a preparatively useful scale (200 mg/injection). α-Hydroxylation of **80** was achieved best by treatment of the lactam enolate (LDA) with TMSO–OTMS[40] and was followed by a direct quench with TIPSOTf providing **82** (64%), Scheme 14 (natural enantiomer shown). More common α-hydroxylation methods including the use of the Davis oxaziridines ((+)-CSO)[41] or MoOPH[46] were not nearly as effective (30–50%). The stereochemistry of the α-hydroxylation was clear from the ^1H NMR spectrum of **82** (C7-H; dd, *J* = 5.5, 11.7 Hz) and unambiguously determined with a X-ray structure determination of the corresponding *p*-bromobenzoate.[23] Conversion of **82** to thioamide **83** (70%) with Lawesson's reagent, reductive desulfurization with Ra–Ni conducted under conditions (THF, 15 h, 23 °C) that also served to cleave the benzyl ether provided **84** (91%), and subsequent acetylation of the resulting secondary alcohol afforded **85** (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 **86** (98%). Silyl ether cleavage (Bu_4NF, THF, 89%) and subsequent secondary alcohol activation and regioselective elimination of **87** (Ph_3P, DEAD, THF, 23 °C) provided either (−)- or *ent*-(+)-vindoline (75%) identical in all respects with authentic material [synthetic natural vindoline $[\alpha]_D^{20}$ −17 (*c* 0.40, $CHCl_3$), lit.[38] $[\alpha]_D^{20}$ −18 ($CHCl_3$)]. The final conversion of **87** to **3** enlisting the newly implemented Mitsunobu activation of the secondary alcohol for elimination proved much more effective and reproducible than alternative procedures that enlist reagents (e.g., Ph_3P–CCl_4)[10,31] that generate reactive nucleophiles (e.g., Cl^-) that can compete with the elimination reaction.

A second total synthesis of vindoline was accomplished utilizing cycloadduct **81** and was conducted while efforts to secure **80** were underway (Scheme 15). 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 **81** (LDA, TMSOOTMS) followed by in situ treatment with TIPSOTf

provided **88** in superb yield (75%). The stereochemistry of the intermediate alcohol, also obtained by a less effective reaction of the lactam enolate with Davis' reagent[41] ((+)-CSO, 40–50%), was established by ^{1}H NMR (C7-H; dd, J = 5.5, 12.1 Hz) and confirmed by X-ray.[23] C4-Alcohol deprotection (H_2, Pd/C, 90%) and oxidation of **89** with TPAP/NMO (81%) or Dess–Martin periodinane (1.2 equiv, pyr–CH_2Cl_2, 0 °C, 30 min, 86%) provided **90**. Thiolactam formation (Lawesson's reagent, 81%) and Ra–Ni desulfurization of **91** (THF, 25 °C, 78%) provided **92**. The alternative sequence of converting the amide **88** to the corresponding thioamide with Lawesson's reagent (toluene, reflux, 60%) and its reductive removal with Ra–Ni concurrent with *O*-debenzylation (THF, reflux, 10 h, 60–80%) was followed by a more problematic oxidation (TPAP/NMO; SO_3–Py, Et_3N, DMSO) of the secondary alcohol to ketone **92** in the presence of the newly liberated tertiary amine (N8). Diastereoselective reductive oxido bridge cleavage of **92** (H_2, PtO_2, MeOH, H^+)[13] furnished **93** (82%), TIPS ether cleavage (Bu_4NF, THF, 98%), and treatment of **94** with Ph_3P–DEAD led to activation and elimination of the C7 alcohol to provide **95** (62%). Following the protocol of Buchi,[9a] diastereoselective C4 carbonyl reduction of **95** (Redal-H, $AlCl_3$) and subsequent acetylation (Ac_2O, 83%) of deacetylvindoline (**96**) furnished vindoline (**3**). Notably, this latter route proceeded through desacetylvindoline (**96**), which itself is a naturally occurring alkaloid being the penultimate biosynthetic intermediate to vindoline.[48]

6,7-Dihydrovindoline

Although not a natural product itself, 6,7-dihydrovindoline (**8**) constitutes a historically important, characterized derivative of vindoline that assisted in the original structure determination.[5] Moreover, similar semisynthetic dihydro derivatives of vinblastine and its analogues were explored in early studies, albeit with conclusions that they are active, but less efficacious in vivo.[49] Today this conclusion would be worth revisiting given the apparent lack of direct role that the $\Delta^{6,7}$-alkene appears to have on the interaction of vinblastine with its biological target.[50] Anticipating that the approach detailed herein may be utilized to provide synthetic vinblastine analogues containing deep-seated changes in the vindoline subunit, we elected to extend the studies to a synthesis of **8**. Notably, removing the requirement for introduction of the $\Delta^{6,7}$-alkene eliminates 3–4 steps from the route and provides an extraordinarily short synthesis of such vindoline analogues.

Consequently, a remarkably concise synthesis of 6,7-dihydrovindoline (**8**) was developed enlisting the cascade cycloadduct **80**. Thus, reductive removal of the *O*-benzyl ether (H_2, Pd $(OH)_2$, MeOH, 23 °C, 24 h, 85%) and *O*-acetylation of the newly liberated secondary alcohol **97** (Ac_2O, pyr, 23 °C, 16 h, 88%) provided **98** (Scheme 16, natural enantiomer shown). Treatment of **98** with Lawesson's reagent (toluene, 90 °C, 2 h, 97%) followed by reductive removal of the thiolactam with Ra–Ni (THF, 23 °C, 2 h) and a final reductive oxido bridge cleavage of **100** (H_2, PtO_2, 1:1 MeOH–EtOAc, 65% for two steps) provided 6,7-dihydrovindoline [synthetic natural enantiomer of **8**, $[\alpha]_D^{23}$ +37 (*c* 0.75, $CHCl_3$) and +12 (*c* 0.4, MeOH)]. Authentic **8**, ($[\alpha]_D$23 +37 (*c* 0.75, $CHCl_3$) and +13 (*c* 0.70, MeOH)) prepared by hydrogenation of a sample of naturally occurring vindoline (H_2, Pd/C, MeOH, 25 °C, 20 h, 98%), proved indistinguishable from synthetic (+)-**8**.

An alternative to this approach was also developed that employed the more accessible cycloadduct **81** derived from (*E*)-**79**. Thus,*O*-debenzylation of **81** (H_2, $Pd(OH)_2$, MeOH, 23 °C, 50 psi, 93%) and oxidation of the liberated alcohol **101** (Dess–Martin periodinane, pyr, CH_2Cl_2, 0–25 °C, 30 min, 92%) provided ketone **102** (Scheme 17, natural enantiomer shown). Notably, this oxidation carried out in pyridine proved much more effective than TPAP (0.1–1.0 equiv, NMO, CH_2Cl_2, 23 °C, 2–24 h, 30–60%) and may benefit from the use of the basic solvent. Thiolactam formation by treatment of **102** with Lawesson's reagent (toluene, 90 °C, 2h, 70%) followed by its reduction with Ra–Ni (THF, 23 °C, 1 h, 75%) provided **104**. Reductive

oxido bridge cleavage (H_2, PtO_2, MeOH–EtOAc, cat. HCl, 23 °C, 50 psi, 81%) required acid catalysis and provided **105** in good conversions. The alternative sequence of treatment of **81** with Lawesson's reagent to provide thioamide **106** (88%), its reductive removal with Ra–Ni under conditions that also resulted in *O*-debenzylation (THF, 65 °C, 60%), and subsequent oxidation of **107** (Dess–Martin periodinane, 15%) to provide **104** was less straightforward suffering from a problematic oxidation of the secondary alcohol in the presence of the newly liberated tertiary amine. Ketone **105** has been converted to **8** previously[9b] and it also constitutes a key, late stage intermediate in the Kutney total synthesis of vindoline.[9b]

4-Desacetoxyvindoline

Having established the synthetic approach to vindoline (**3**) and by virtue of the opportunities this provides for the preparation of simpler derivatives, we elected to illustrate this with the preparation of 4-desacetoxyvindoline (**9**). This alkaloid is a key, naturally occurring[51] and late stage biosynthetic precursor to vindoline requiring only C4 hydroxylation[48] and subsequent acetylation. Despite this important role in the biosynthetic pathway to vindoline, we are not aware of a total synthesis of **9** and to date it has only been characterized by MS and ^{1}H NMR.[51] Moreover, we are aware of only one report[52] of its attempted preparation through the degradation of vindoline and, by virtue of the route used, the modified C3 stereochemistry was apparently inverted[51a] providing 3-epi-4-desacetoxyvindoline. This lack of preceding work is especially surprising given the historical importance of desacetoxyvinblastine[49] lacking only this vindoline C4 acetoxy group. This natural product is equipotent or more potent in vitro and exhibits comparable or enhanced in vivo efficacy compared to vinblastine, but it is present in even lower natural abundance (>10-fold less) than vinblastine which itself is found in trace amounts (≤0.00025% of dry leaf weight).

Importantly, this extension of the approach to include the total synthesis of 4-deacetoxyvindoline (**9**) is straightforward, and was projected to be much easier to implement requiring a simpler, more reactive disubstituted (vs trisubstituted) tethered dienophile. Thus, N-acylation of 1,3,4-oxadiazole **78** with 4-ethyl-4-pentenoic acid[19] (**17**, EDCI, DMAP, CH_2Cl_2, 23 °C, 16 h) provided the cycloaddition substrate **109** (85%). Consistent with expectations, warming **108** in *o*-dichlorobenzene (180 °C, 24 h, 74%) or triisopropylbenzene (TIPB, 230 °C, 18 h, 83%) cleanly provided **109** as a single detectable diastereomer (Scheme 18, natural enantiomer shown) that was readily resolved on a semipreparative ChiralCel OD column (2 × 25 cm, 10% EtOH–hexane, 10 mL/min, t_R (natural) = 21.4 min and t_R (unnatural) = 29.3 min, α = 1.37). Without a rotation of the natural product with which to compare synthetic samples, the absolute configuration of **109** was established by X-ray analysis of **110**[23] ($[\alpha]_D$23 +131 (*c* 0.6, $CHCl_3$), recrystallized from Et_2O, mp 228–231 °C), a heavy atom derivative prepared by treatment of (+)-**109** ($[\alpha]_D$23 +129 (*c* 0.7, $CHCl_3$)) with NBS (2.5 equiv, THF, –30 °C, 30 min, 94%). α-Hydroxylation of **109** (NaHMDS, TMSOOTMS, 62%), protection of the secondary alcohol **111** as its TIPS ether **112** (TIPSOTf, Et_3N, 25 °C, 1 h, 91%), conversion to the thioamide **113** (69%) with Lawesson's reagent, and its reductive removal with Ra–Ni (THF, 23 °C, 1 h, 97%) provided **114**. Diastereoselective reductive oxido bridge cleavage of **114** (H_2, PtO_2, EtOAc–MeOH, 88%) followed by TIPS deprotection of **115** (Bu_4NF, THF, 23 °C, 30 min, 97%) and regioselective elimination of the secondary alcohol **116** enlisting Ph_3P–DEAD (71%) provided 4-deacetoxyvindoline (**9**) which was fully characterized for the first time [natural **9**: $[\alpha]_D$[23] +33 (*c* 0.6, $CHCl_3$)].

4-Desacetoxy-6,7-dihydrovindoline and its 8-oxo derivative. Two analogues of vindoline that contain deep-seated structural changes and that we anticipate incorporating into vinblastine analogues are 4-desacetoxy-6,7-dihydrovindoline (**10**) and its 8-oxo derivative **118**. As alluded to earlier, the C4-acetoxy substituent, which lies at the external solvent exposed face of the vinblastine–tubulin complex,[50] can be removed from vinblastine without diminishing in vitro

potency or in vivo efficacy.[49] Similarly, the $\Delta^{6,7}$-alkene, which makes no apparent key interaction with tubulin,[50] can be removed from vinblastine resulting in only a 2-fold reduction in in vitro potency[49] and exhibiting good in vivo efficacy.[49] These observations suggest that vinblastine analogues containing the modified vindoline **10** and even **118** would be especially timely to examine. Moreover, their 6–7 step (**10**) or 5–6 step (**118**) access using the cycloaddition cascade described herein highlights the power of the approach and just how accessible such simplified, synthetic analogues of vinblastine bearing deep-seated vindoline modifications may now become.

Thus, treatment of the cycloadduct **109** with Lawesson's reagent (toluene, 110 °C, 1.5 h, 90%), and its *S*-methylation (Me_3OBF_4, CH_2Cl_2) and subsequent reductive removal under conditions ($NaBH_4$, MeOH, 23 °C, 2 h) that also result in reductive oxido bridge cleavage provided 4-desacetoxy-6,7-dihydrovindoline (**10**), $[\alpha]_D^{23}$ +43 (*c* 1.8, MeOH), in superb conversions (92%), Scheme 19 (natural enantiomer shown). Alternatively, reductive oxido bridge cleavage of **109** ($NaCNBH_3$, HCl–MeOH, 25 °C, 1.5 h, 92%) provided the 8-oxo derivative **118**, $[\alpha]_D^{23}$ +6 (*c* 0.7, MeOH), in a single step.

Conclusions

Full details of the development of a concise total synthesis of (−)- and *ent*-(+)-vindoline is disclosed in which the entire pentacyclic skeleton complete with all substituents and all six stereocenters is assembled in a single step tandem [4+2]/[3+2] cycloaddition cascade of a 1,3,4-oxadiazole (Figure 7). The intramolecular reaction cascade is initiated by an inverse electron demand Diels–Alder reaction of an electron-rich enol ether in which the diene and dienophile substituents complement and reinforce the [4+2] cycloaddition regioselectivity dictated by the linking tether. Loss of N_2 from the initial cycloadduct provides a carbonyl ylide that in turn undergoes a 1,3-dipolar cycloaddition with a tethered indole to provide the vindoline pentacyclic skeleton. Beautifully, the intermediate 1,3-dipole is stabilized by the complementary substitution at the dipole termini derived from the starting oxadizole and the tethered indole dipolarophile complements the [3+2] cycloaddition regioselectivity dictated by the linking tether. The stereochemistry of the cascade cycloadduct is controlled by a combination of the dienophile geometry (C4/C5 stereochemistry) and an exclusive endo indole cycloaddition directed to the dipole face opposite the newly formed fused lactam dictated by the dipolarophile tether.[53] Key issues regarding the scope and stereochemical features of the new cycloaddition cascade were defined in the course of the investigations including the observation of an unusual electronic effect that slows the typically faster [3+2] cycloaddition reaction relative to the initiating Diels–Alder reaction. Recognition of this unusual electronic effect and the impact it has on the rate limiting step of the cycloaddition cascade proved instrumental in implementing conditions that provided direct access to vindoline.

As the studies unfolded, the cycloaddition cascade was enlisted as the key step in the total synthesis of a series of related alkaloids of increasing complexity. Thus, a total synthesis of natural and *ent*-minovine (**4**) was completed in which the confusion surrounding the optical rotation, racemization potential, optical purity, and absolute configuration of the natural product was resolved. Similarly, the first total syntheses of both enantiomers of 4-desacetoxy-6,7-dihydrovindorosine (**5**), and 4-desacetoxyvindorosine (**6**), a late stage biosynthetic intermediate for **7**, were conducted along with efforts that provided a concise and effective 11-step total synthesis of (−)- and *ent*-(+)-vindorosine (**7**) complementing the prior two total and six formal total syntheses of this natural product.[39] In efforts that highlight the versatility of the approach and its potential for accessing vinblastine analogues incorporating deep-seated structural changes not accessible from the natural product itself, the cycloaddition cascade was subsequently enlisted in total syntheses of both enantiomers of 6,7-dihydrovindoline (**8**), 4-desacetoxyvindoline (**9**), 4-desacetoxy-6,7-dihydrovindoline (**10**, 7

steps) and its 8-oxo derivative **118** (6 steps). Notably, the preparation of (+)-**9**, constituting its only total synthesis, provided the first opportunity for complete characterization of this natural product which constitutes a key late stage biosynthetic intermediate for vindoline. Finally, the total synthesis of both enantiomers of N-methylaspidospermidine (**11**) was also detailed in efforts that highlight the utility of the cycloaddition cascade for accessing a broader range of alkaloids beyond those immediately related to vindoline. A continued extension of these latter studies to additional alkaloid families is in progress as are efforts directed at vinblastine and key analogues incorporating deep-seated changes in the vindoline subunit.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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35. Prepared by diastereoselective alkylation (NaHMDS, MeI, THF, −78 to −48 °C, 79%) of an Evans optically active N-acyloxazolidinone ((*S*)-3-(4-ethyl-4-pentenoyl)-4-phenyl-1,3-oxazolidin-2-one) followed by hydrolysis (LiOH, H_2O_2, THF–H_2O, 89%).
36. Resubjecting the products to the reaction conditions (*o*-$Cl_2C_6H_4$, 180 °C or TIPB, 230 °C, 24 h) did not result in epimerization of the C7 center (Me substituent) or the detection of cycloreversion products derived from a potentially reversible 1,3-dipolar cycloaddition.
37. Without optimization, substrates **52** and **55** were prepared by treatment of (*S*)-1-amino-2-methyl-4-butene or (*S*)-1-amino-4-ethyl-2-methyl-4-butene with carbonyldiimidazole (85% or 98%) followed by methyl oxalylhydrazide (14, 1 equiv, 1 equiv of HOAc, THF, 40 °C, 18 h, >95% or 91%), subsequent dehydration to the 1,3,4-oxadiazole (1 equiv of TsCl, 2.5 equiv of Et_3N, CH_2Cl_2, 25 °C, 16 h, 77% or 67%) and N-acylation with 2-(N-methylindol-3-yl)acetic acid via its mixed anhydride with Me_3CCOCl (1 equiv, 1 equiv of Et_3N, THF, 0 °C, 30 min) employing the lithium anion of the amino-1,3,4-oxadiazole (1 equiv of *n*-BuLi; THF, −78 °C, 1.5 h, 46% or 70%).
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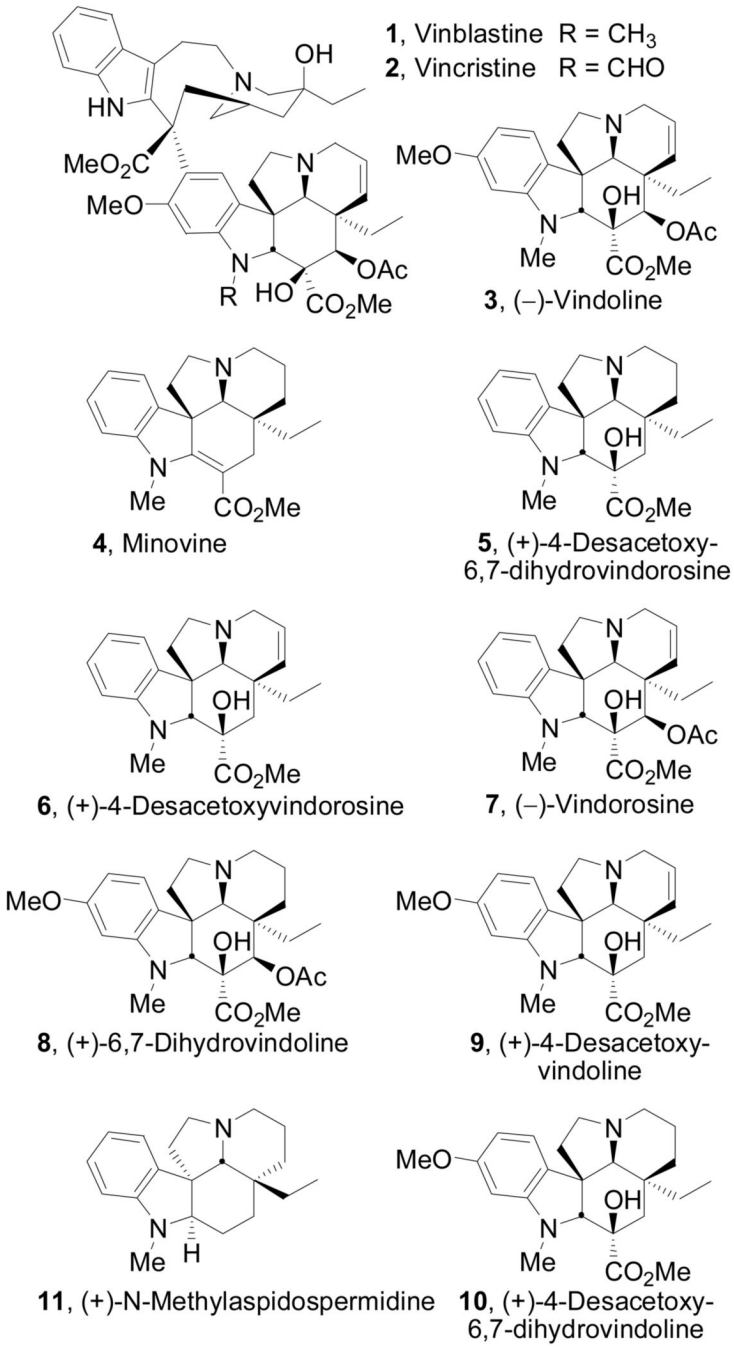


Figure 1.
Natural products and related structures.

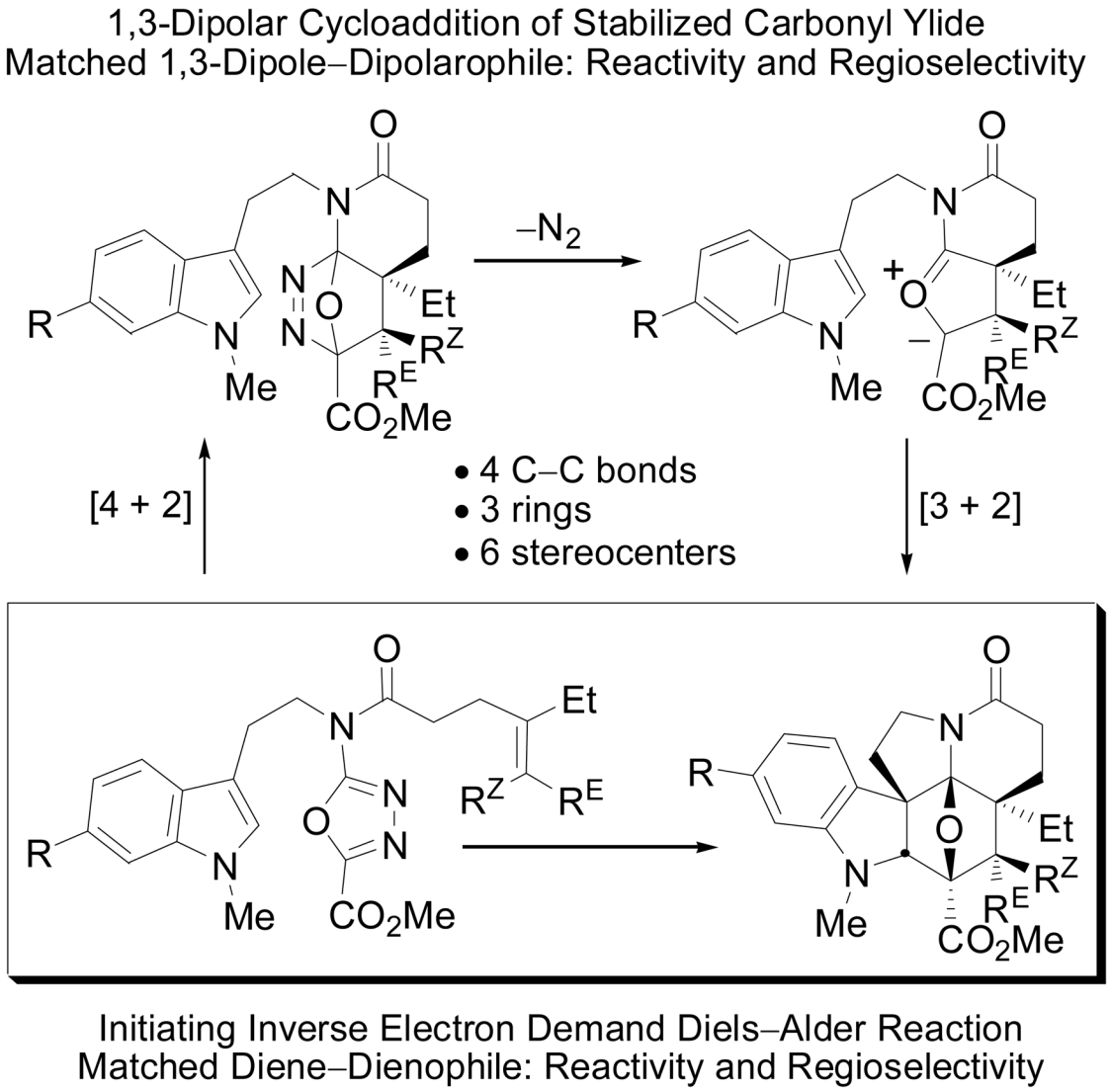
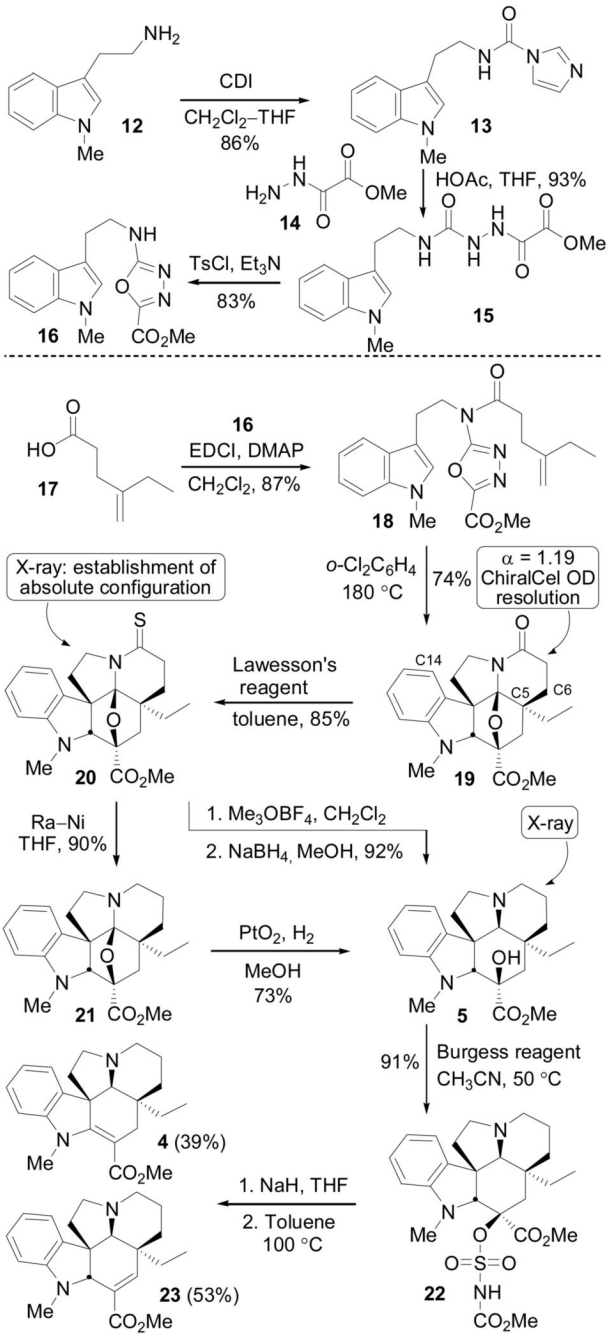
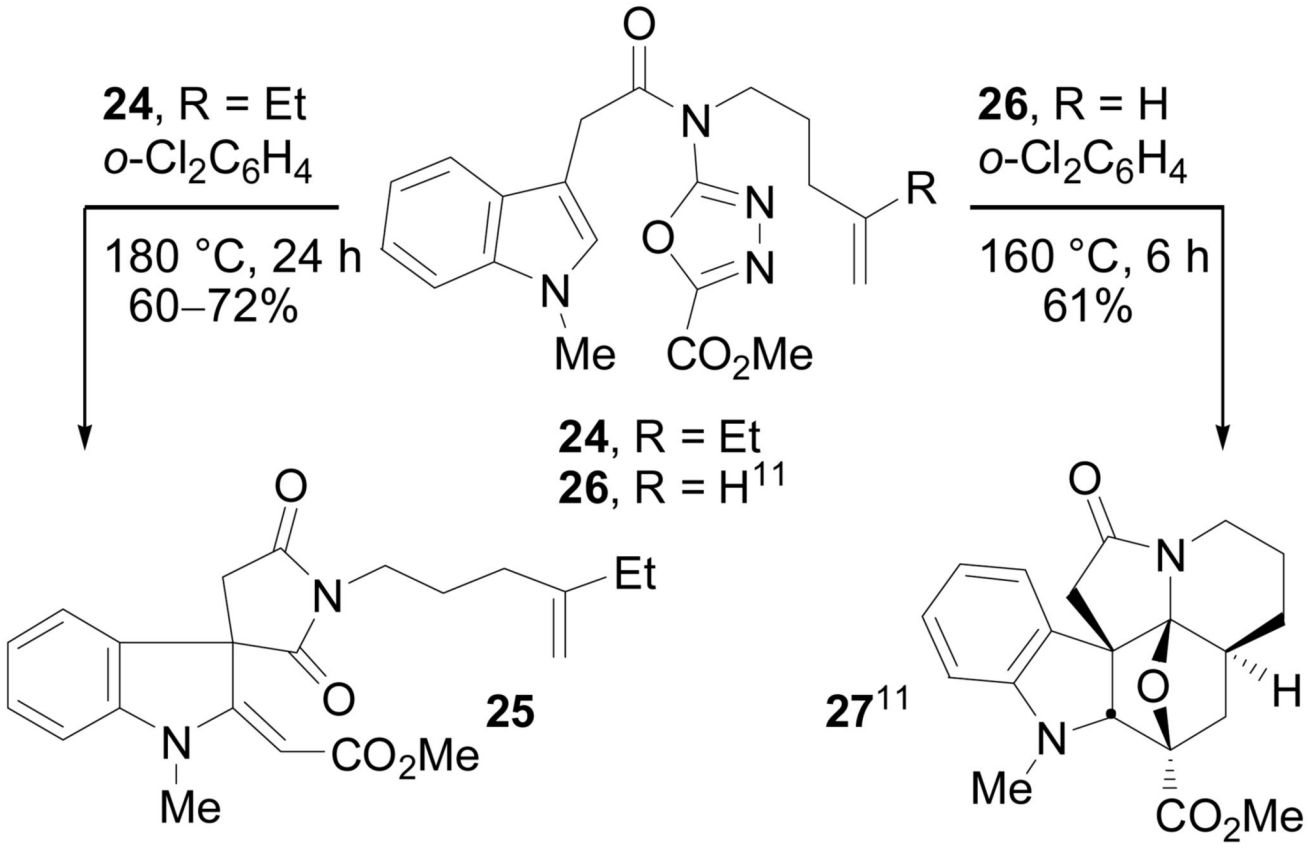


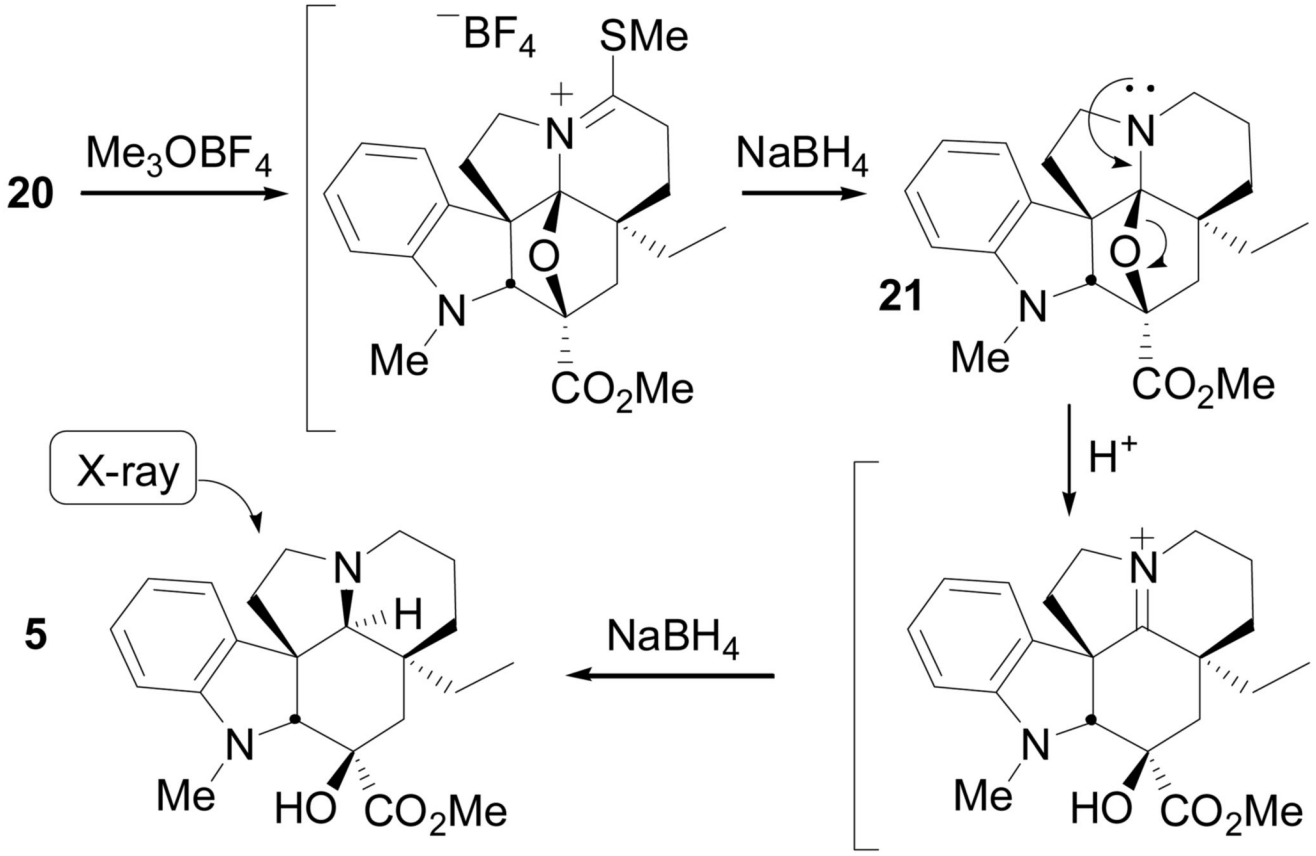
Figure 2.
Key cycloaddition cascade.



Scheme 1.



Scheme 2.



Scheme 3.

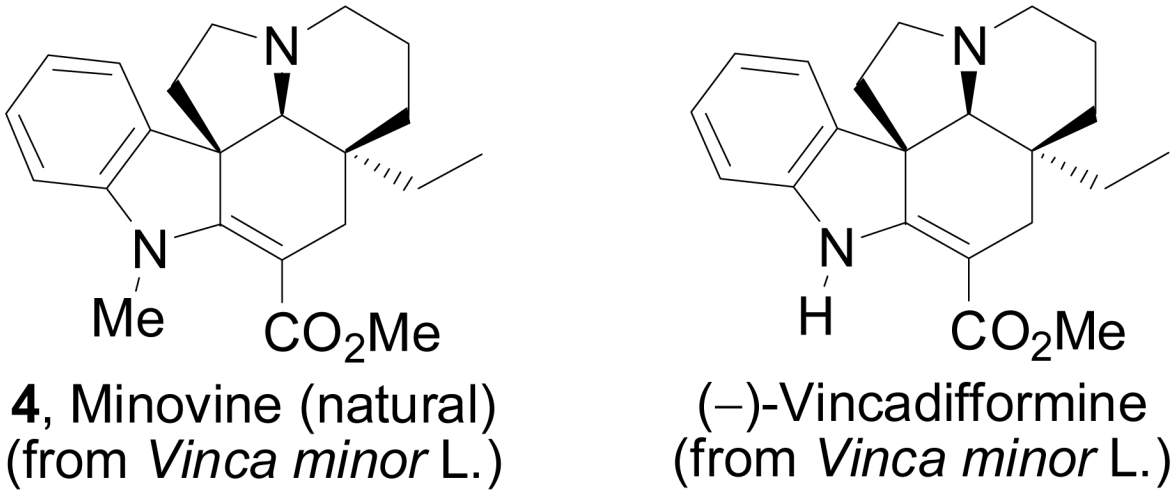
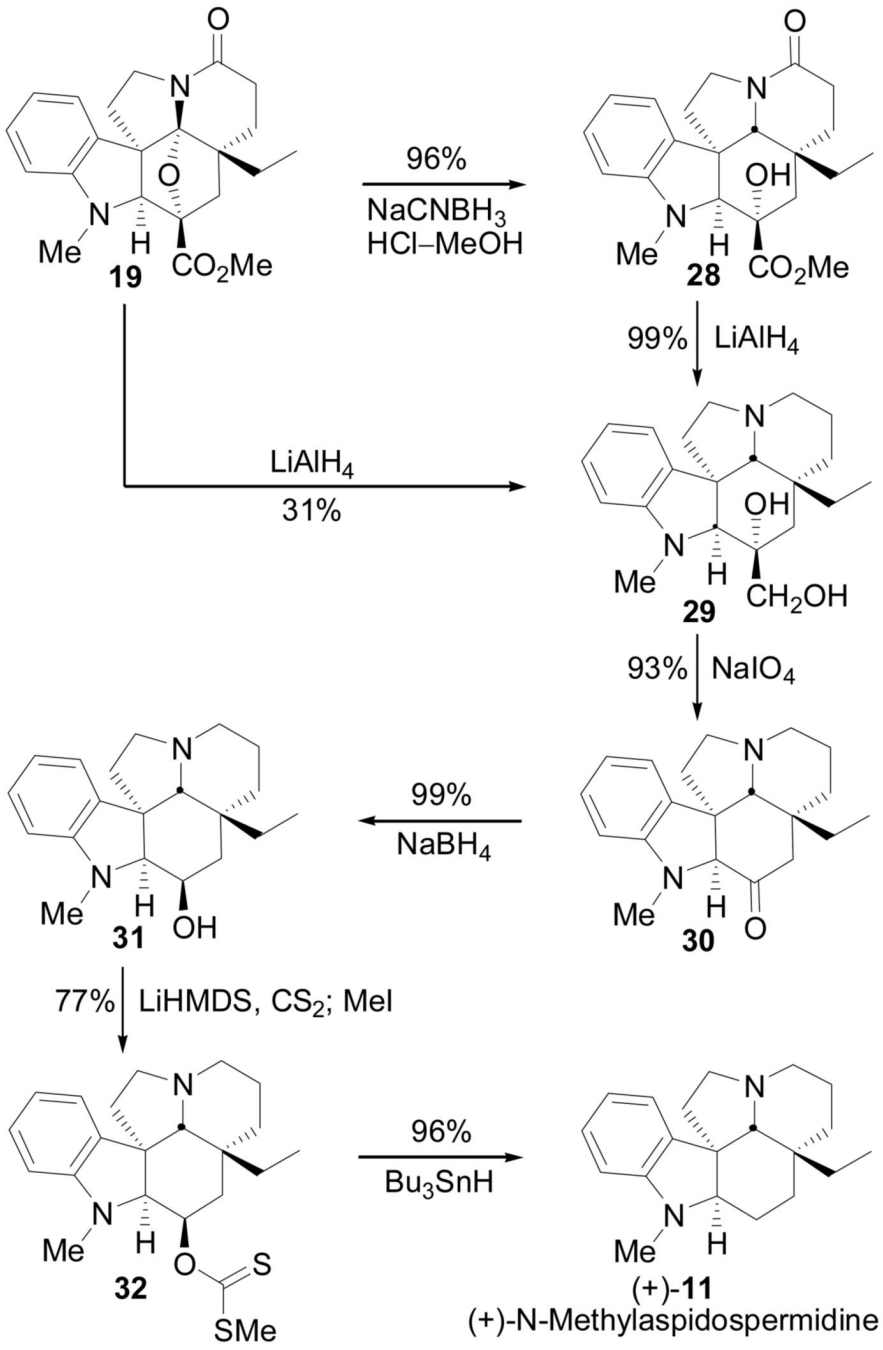
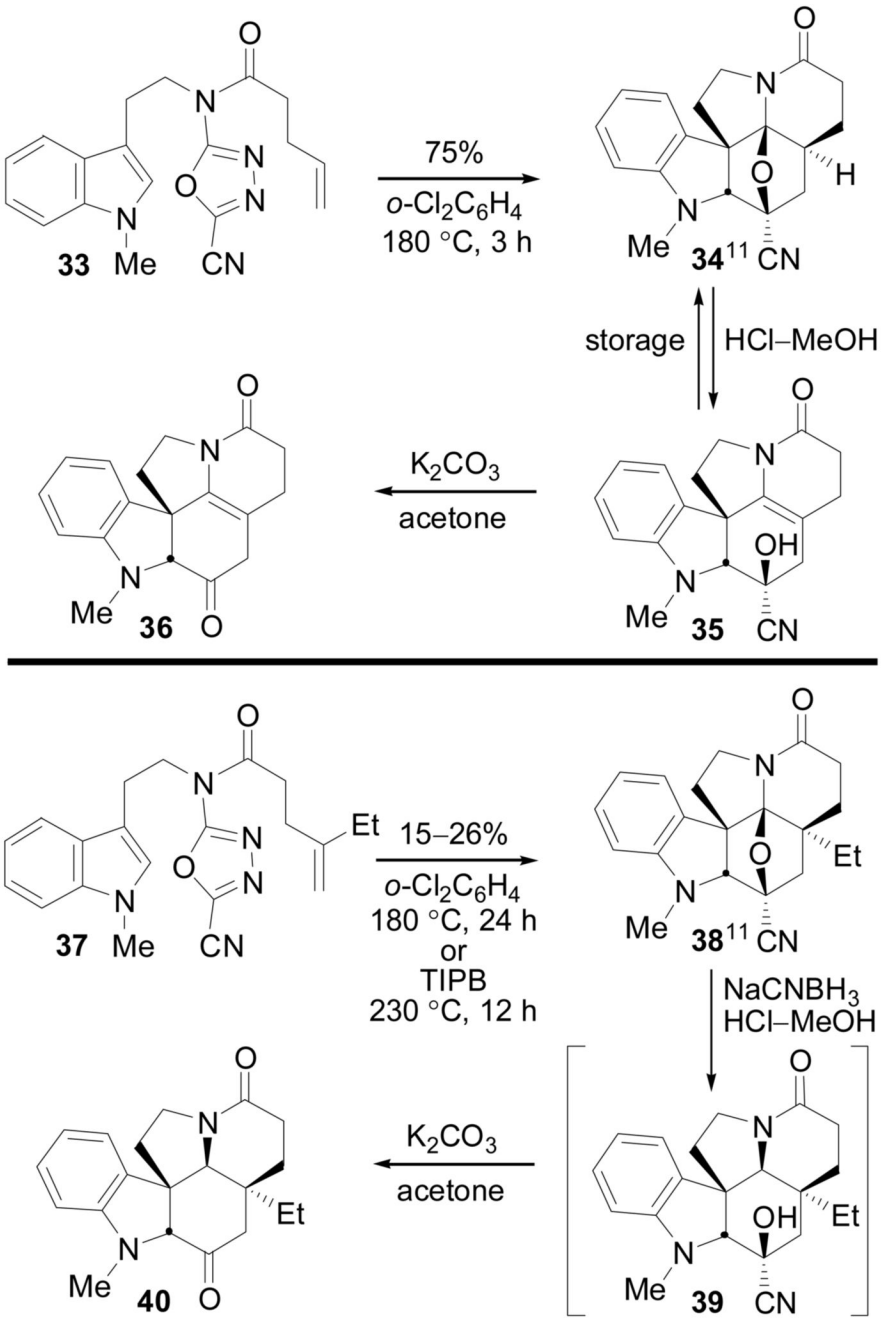


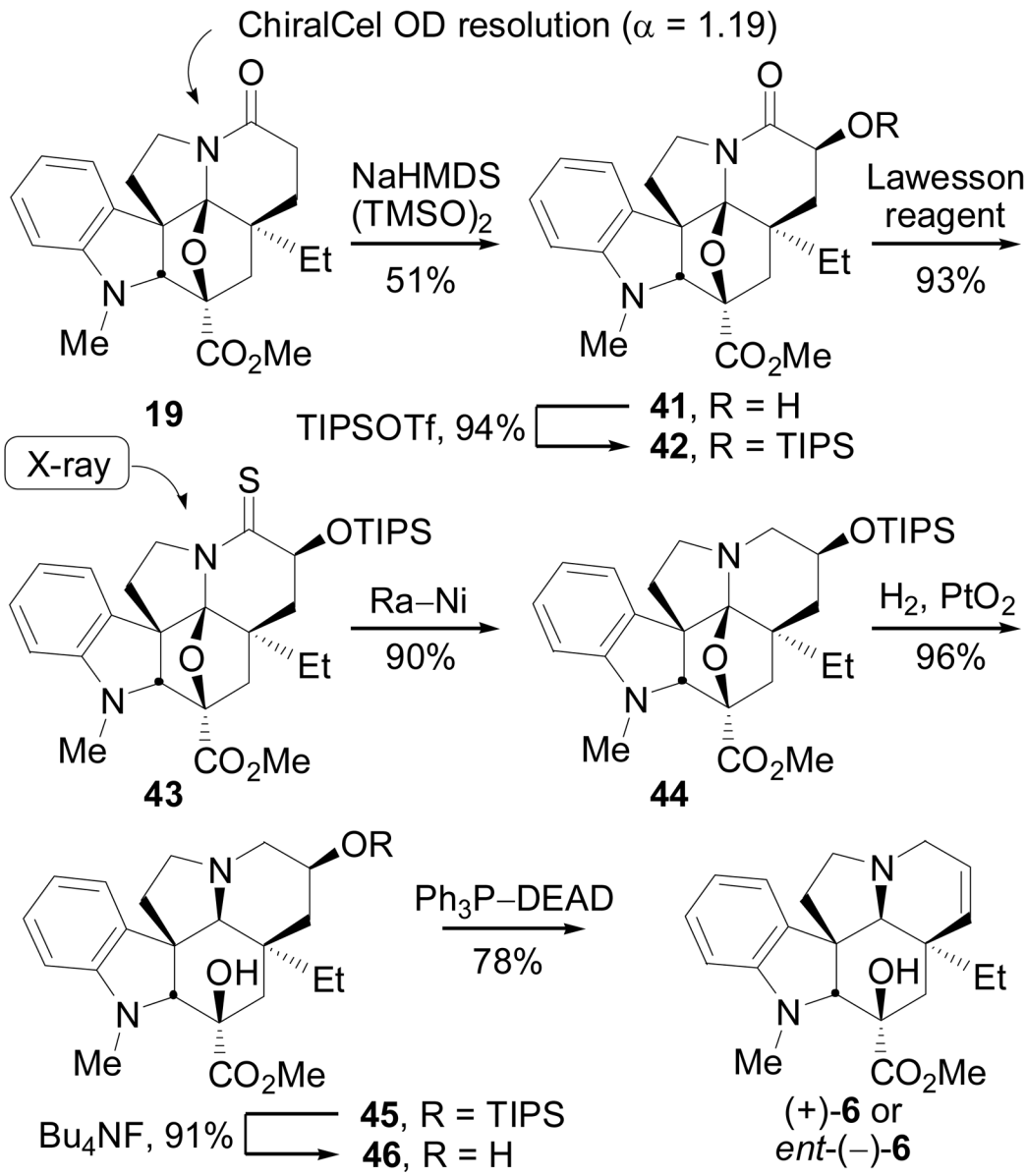
Figure 3.
Absolute configuration of natural products.



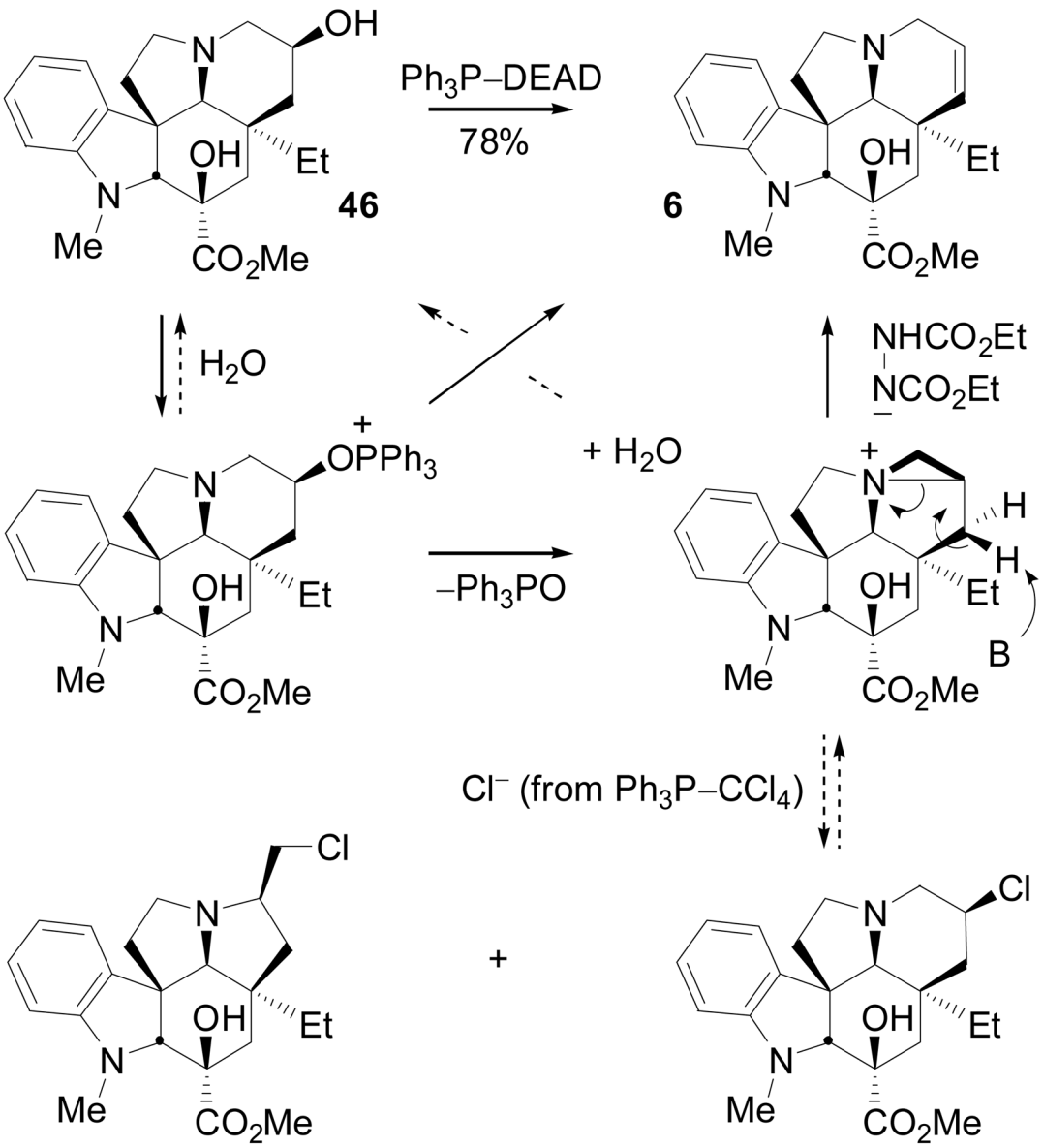
Scheme 4.



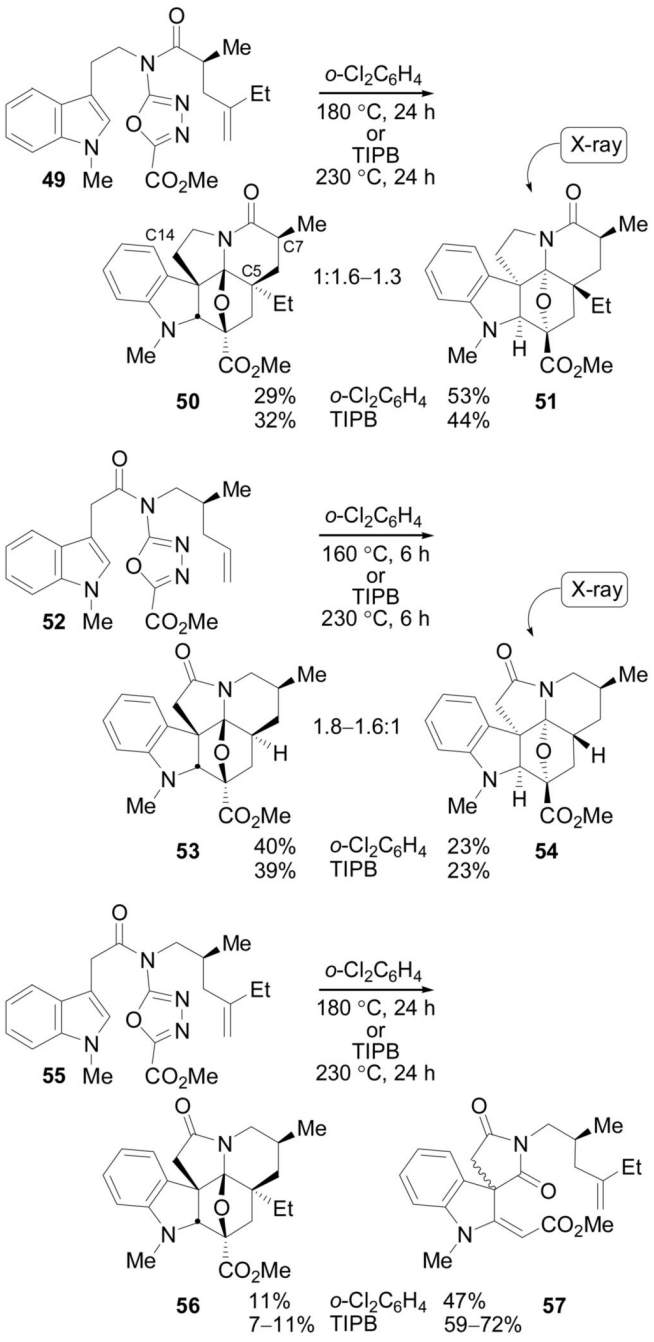
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

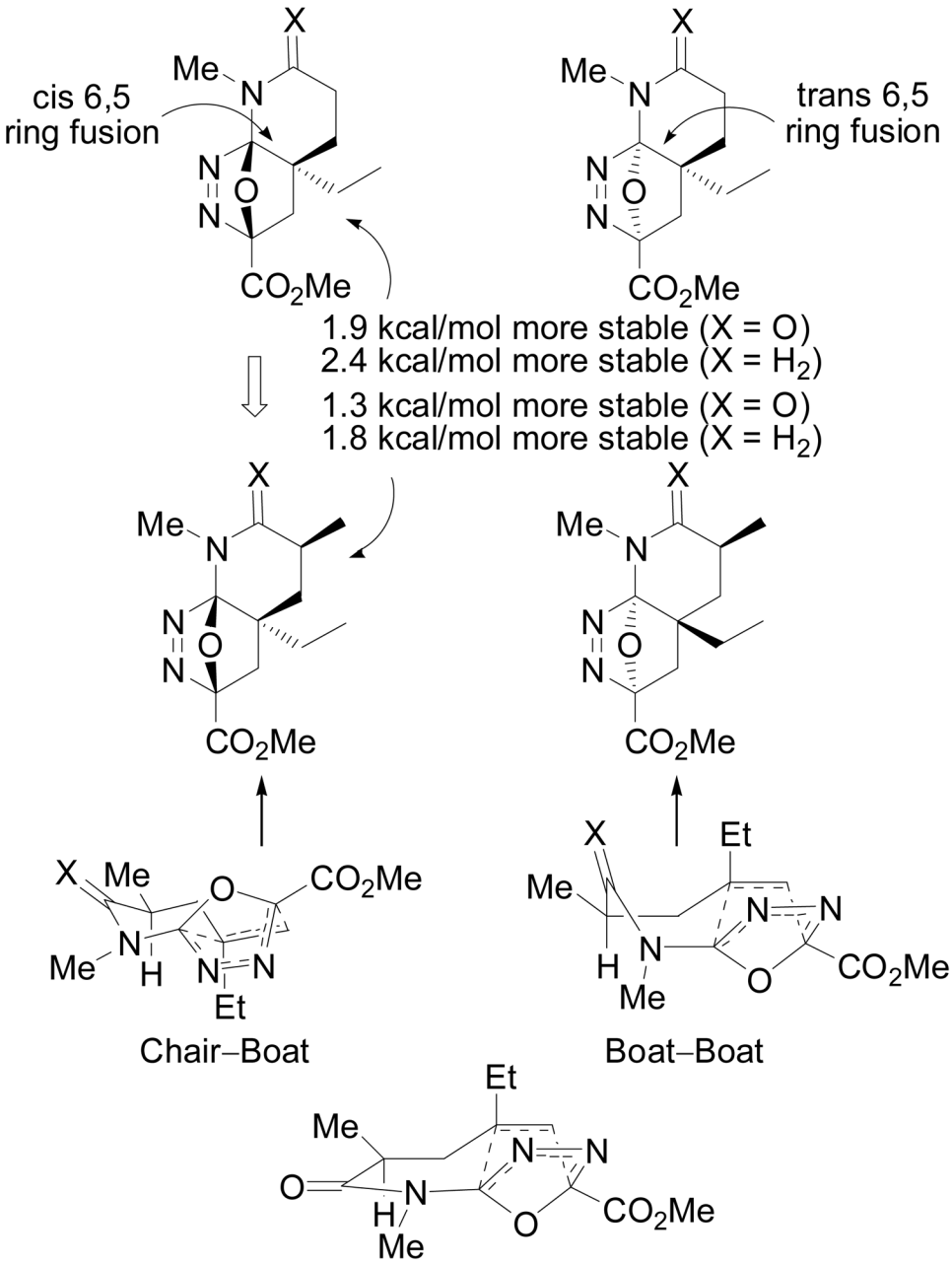
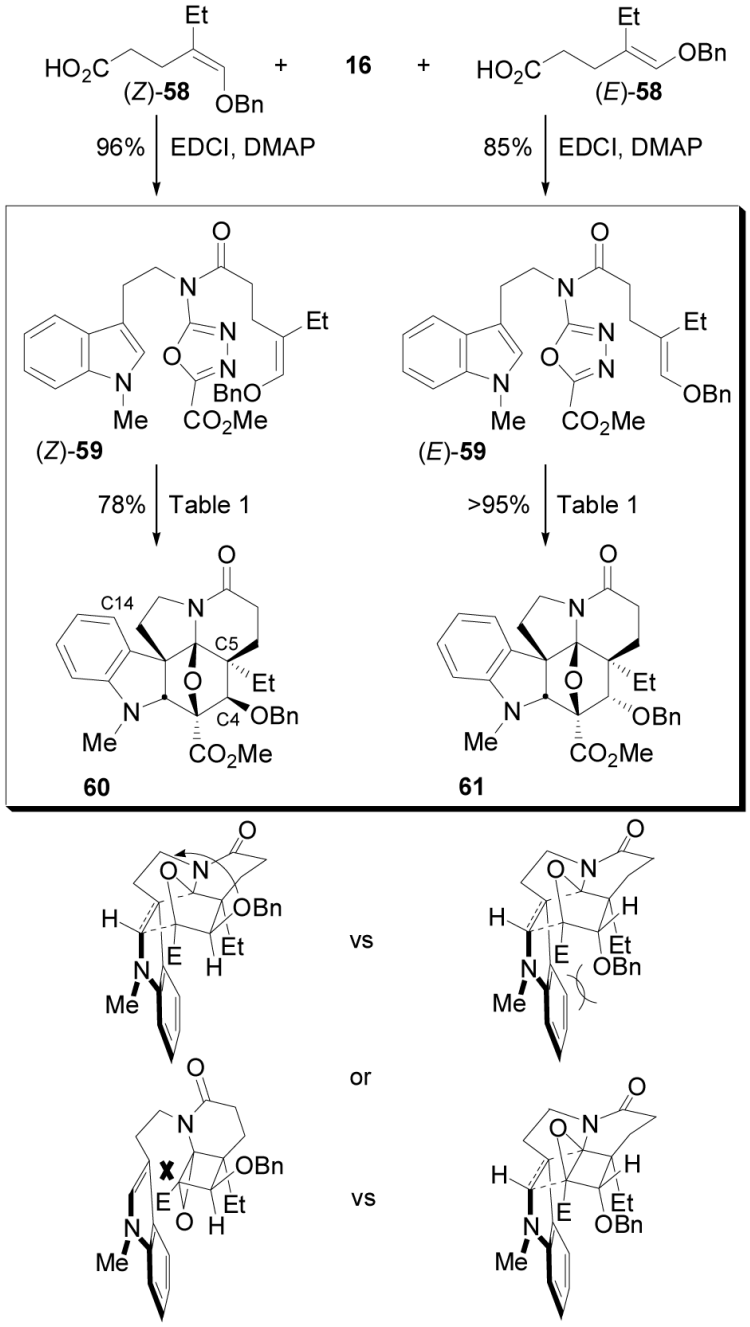
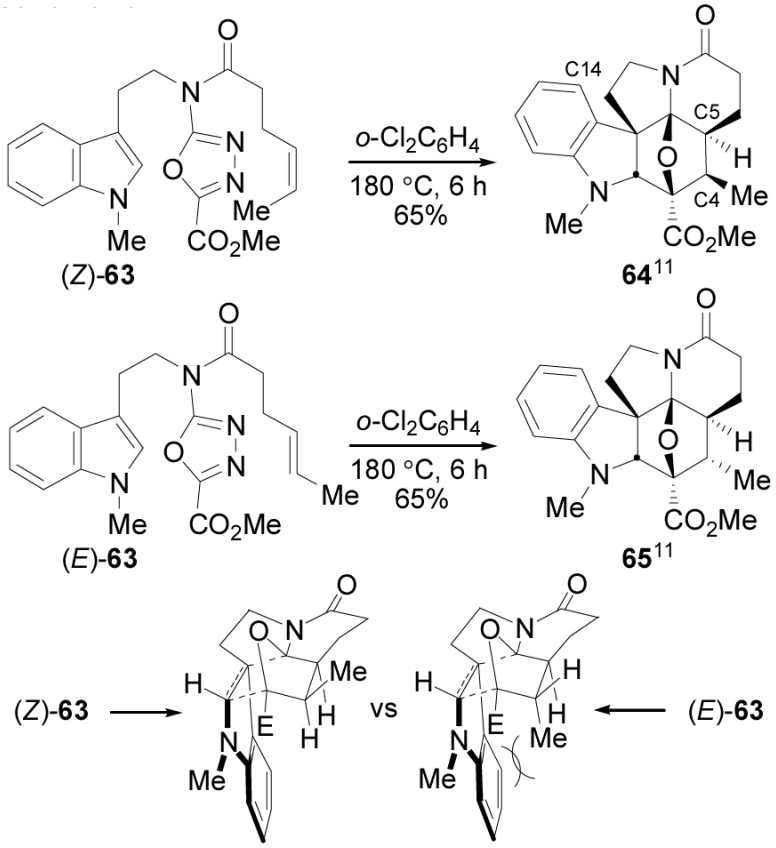


Figure 4.
Competing transition states.



Scheme 9.



Scheme 10.

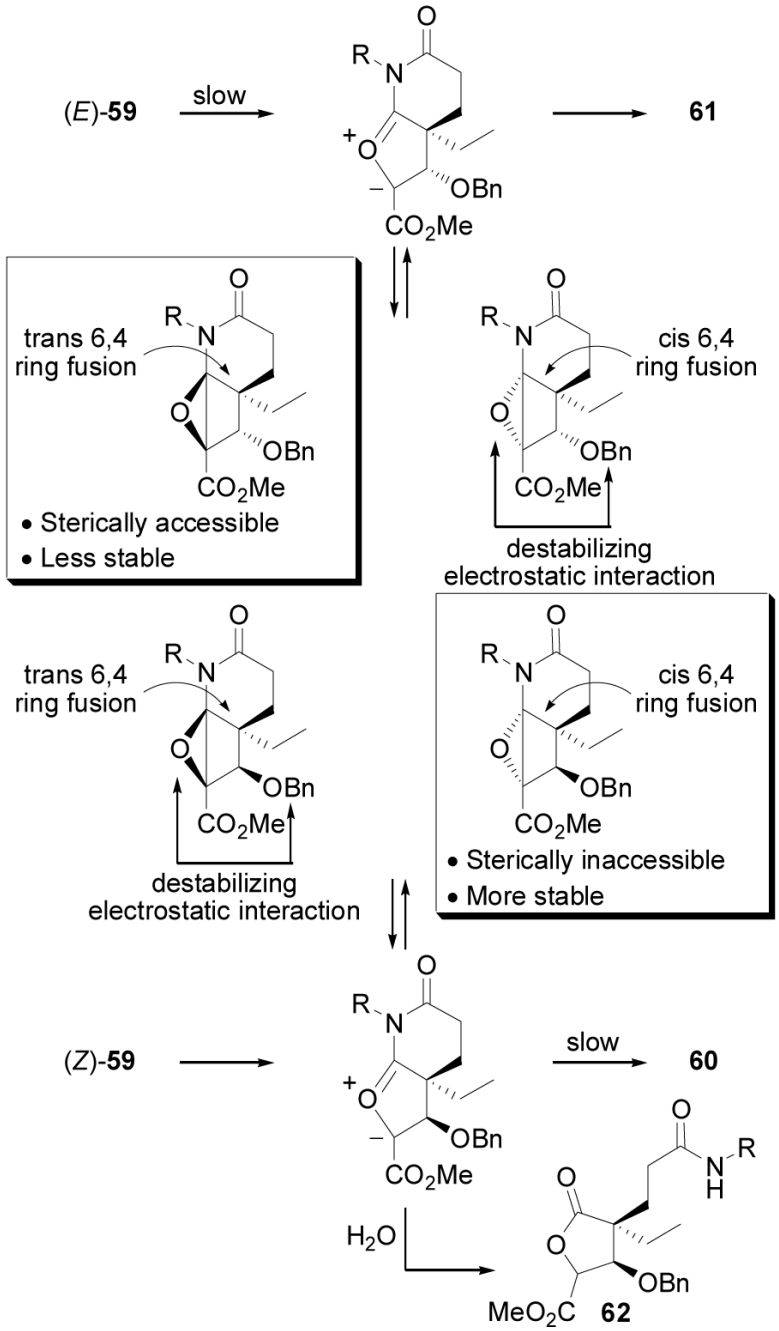
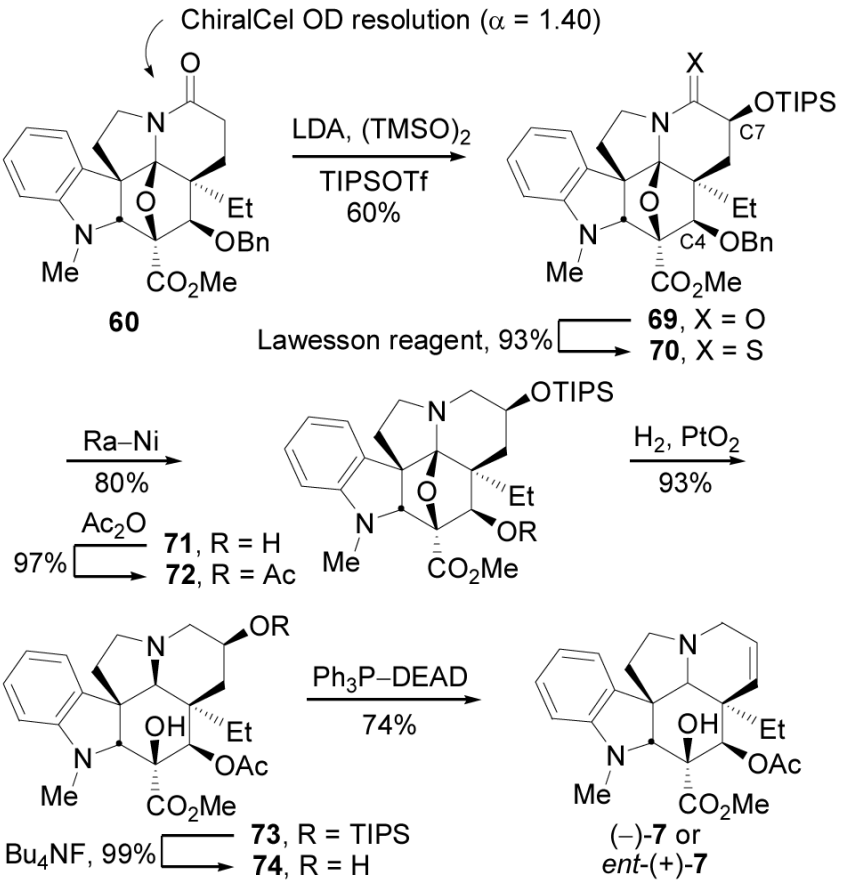
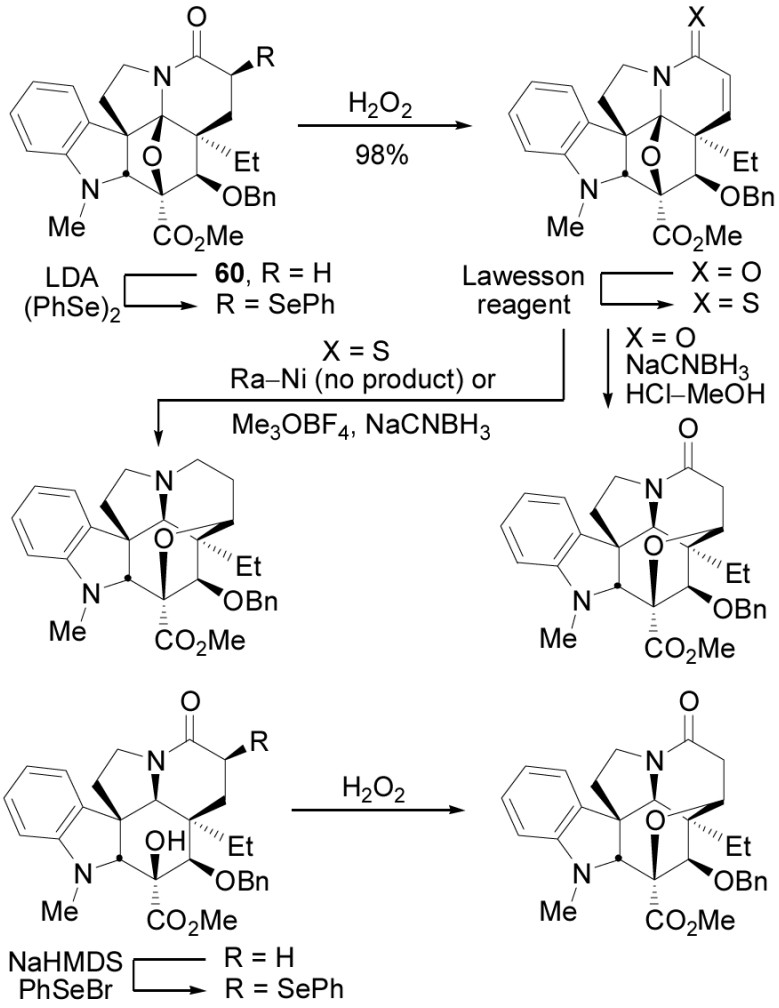


Figure 5.
Cyclobutene epoxides as potential intermediates.



Scheme 11.



Scheme 12.

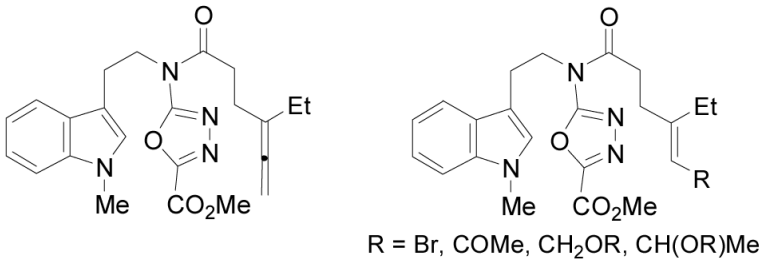
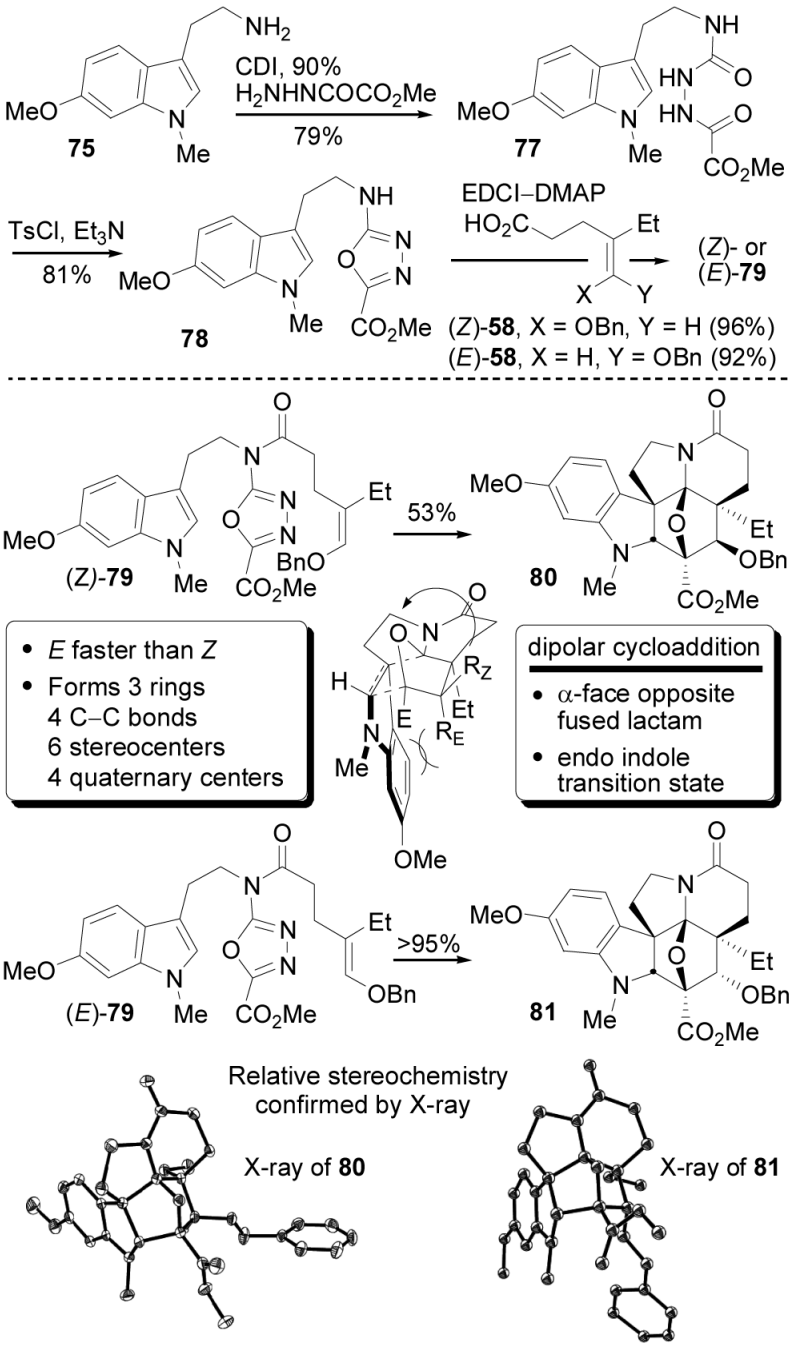
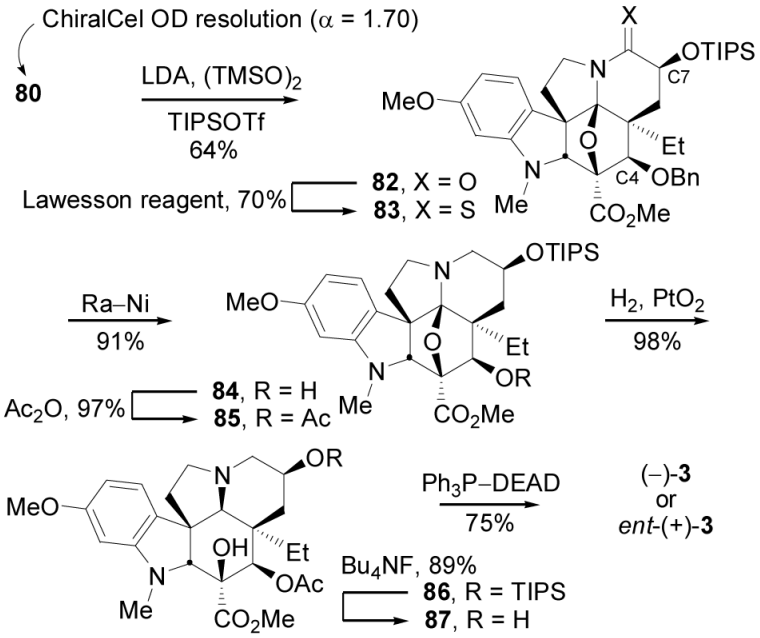


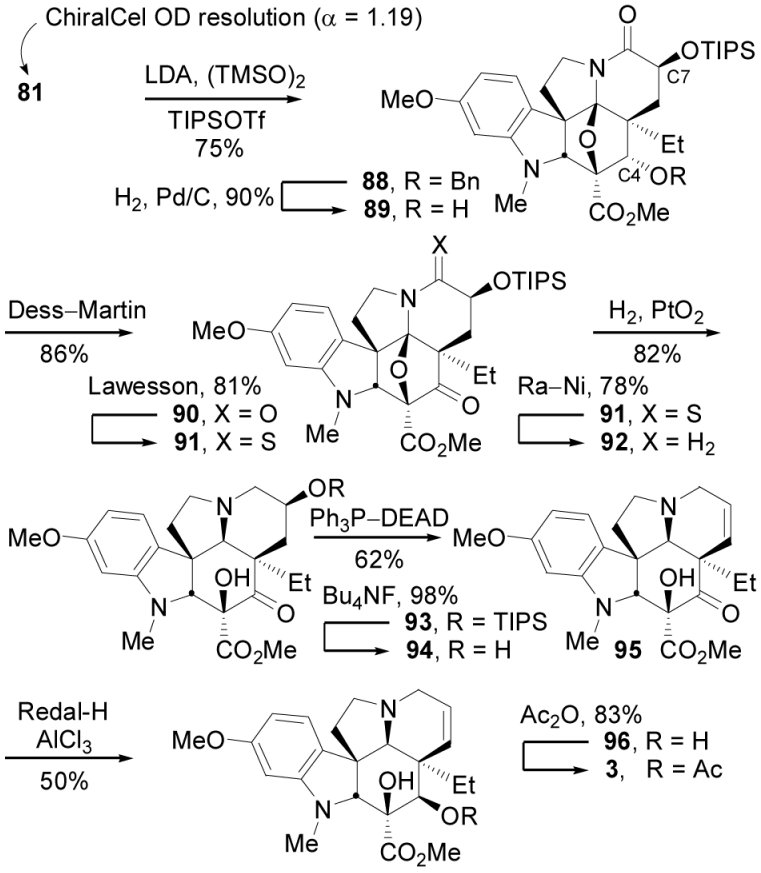
Figure 6.
Additional tethered dienophiles examined.



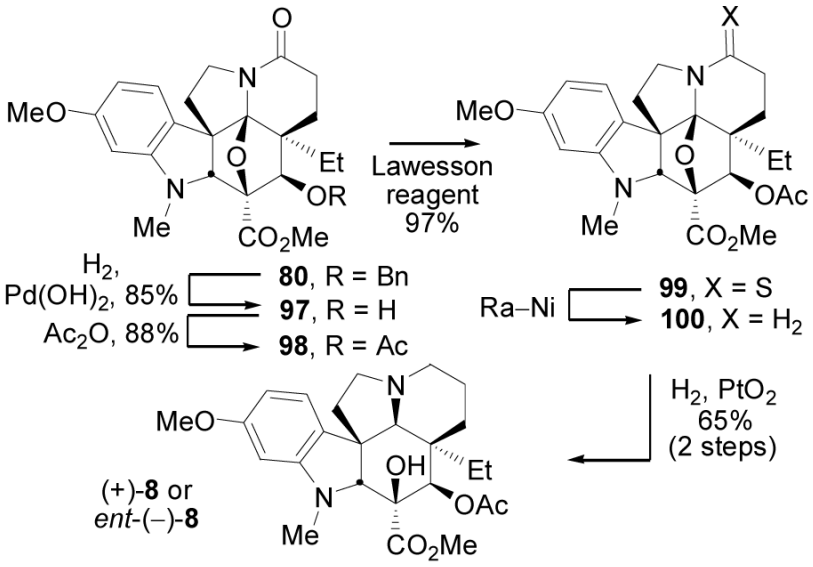
Scheme 13.



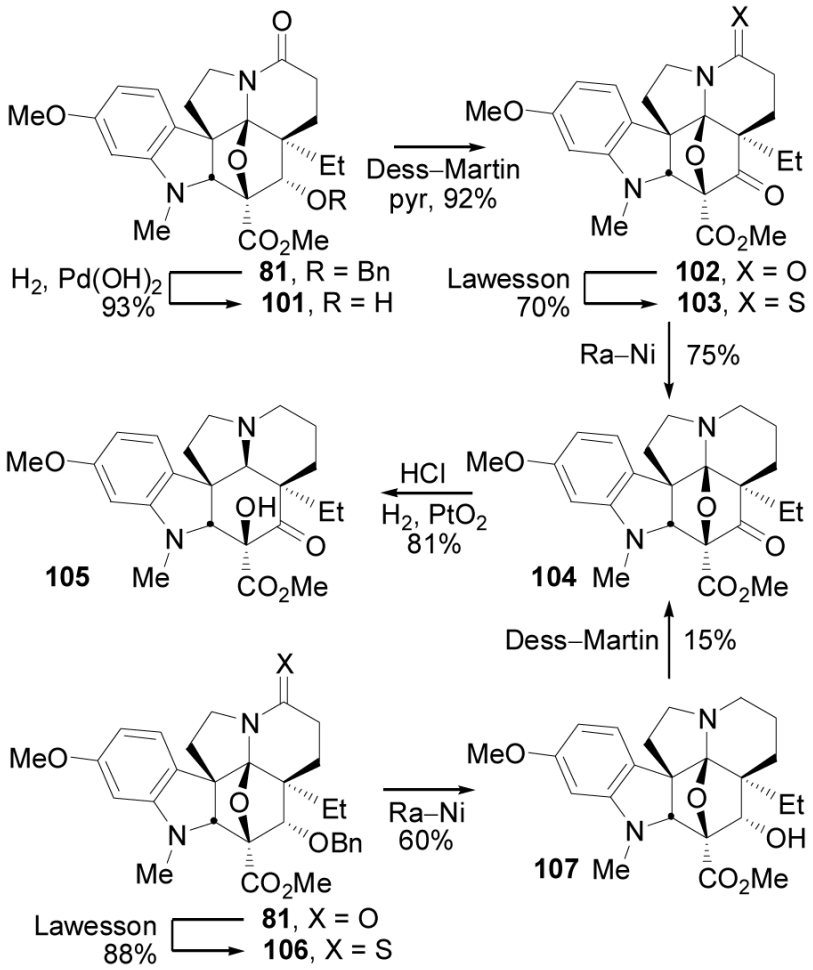
Scheme 14.



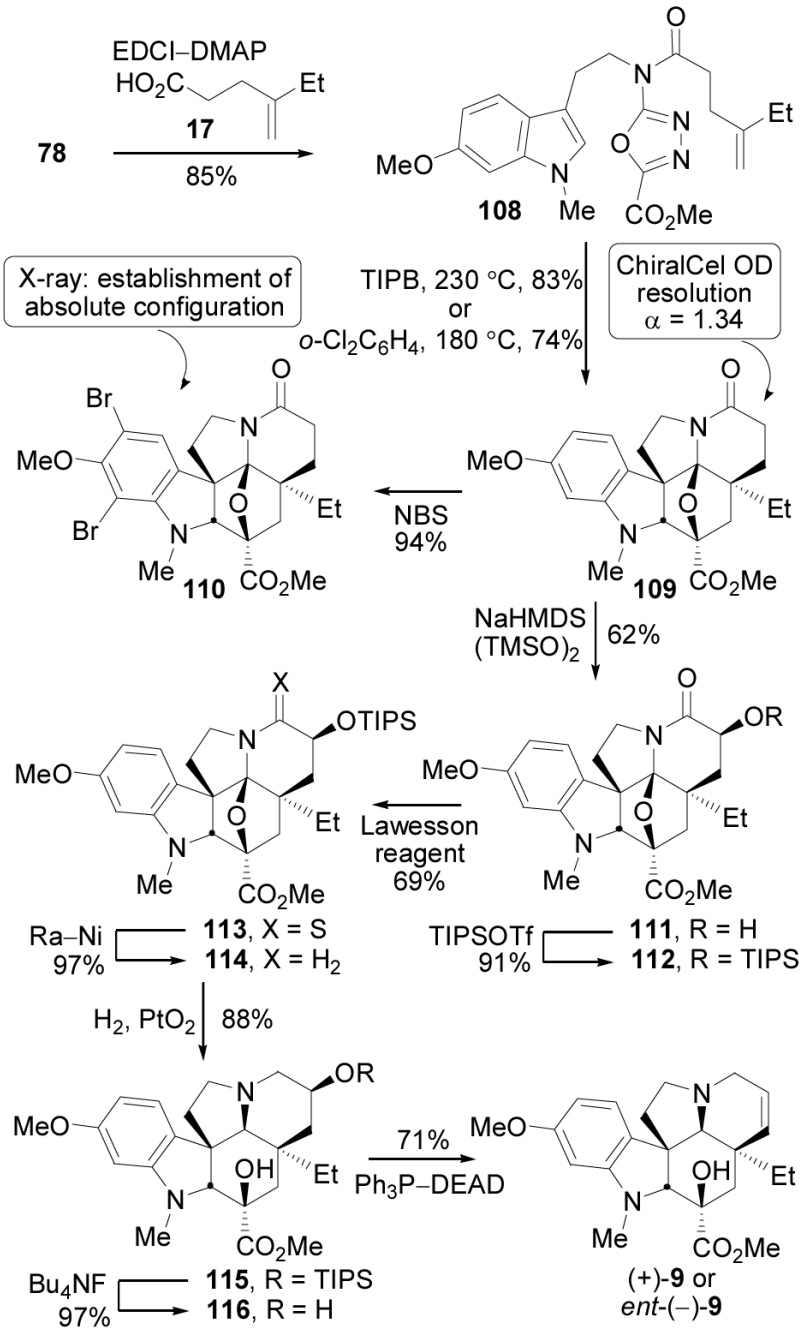
Scheme 15.



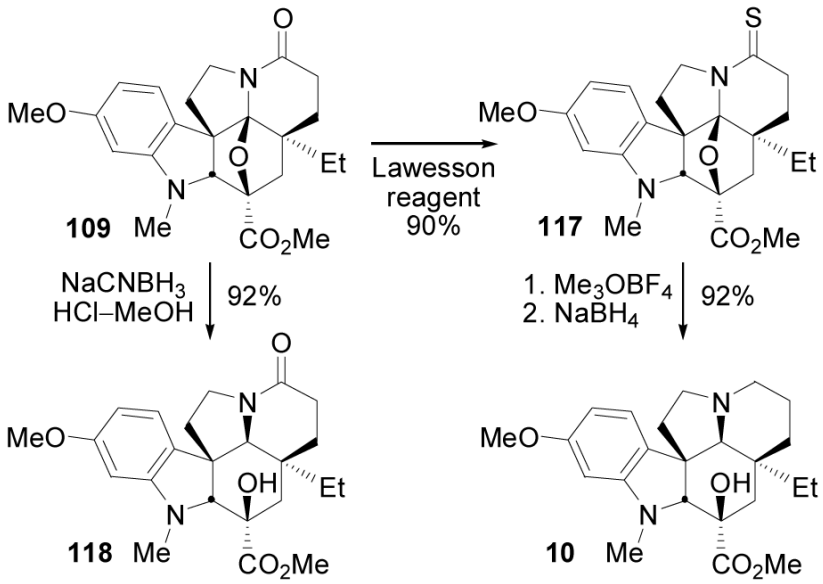
Scheme 16.



Scheme 17.



Scheme 18.



Scheme 19.

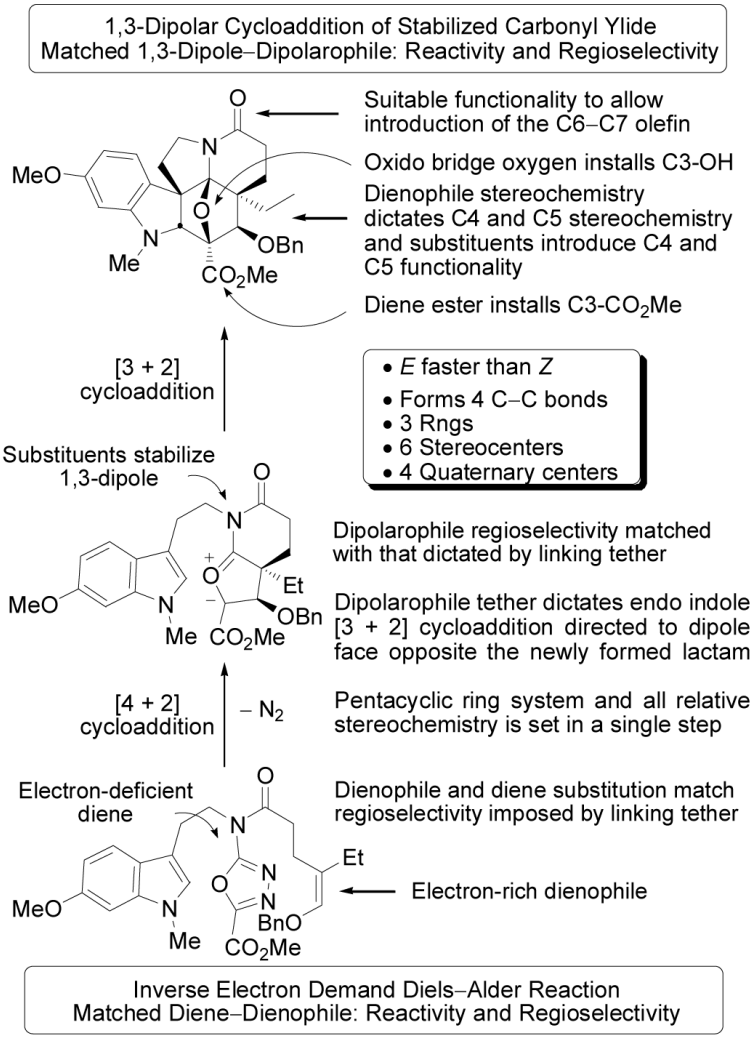


Figure 7.
Highlights of the approach.

Table 1

Cycloaddition Concentration Dependence (**59**).

compound	conc. (mM)	% yield 60 or 61
(*Z*)-**59**[a]	5	30
(*Z*)-**59**[a]	1	39
(*Z*)-**59**[a]	0.75	48
(*Z*)-**59**[a]	0.50	55
(*Z*)-**59**[a]	0.25	63
(*Z*)-**59**[a]	0.10	78
(*E*)-**59**[b]	50	40
(*E*)-**59**[b]	10	47
(*E*)-**59**[b]	5	56 (50–86)[c]
(*E*)-**59**[b]	1	76
(*E*)-**59**[d]	100	33
(*E*)-**59**[d]	50	52
(*E*)-**59**[d]	10	59
(*E*)-**59**[d]	5	64
(*E*)-**59**[d]	1	>95

[a] 230 °C, TIPB, 60 h.

[b] 180 °C, *o*-$Cl_2C_6H_4$, 24 h.

[c] Preparative scale, multiple runs.

[d] 230 °C, TIPB, 18 h.

Table 2

Cycloaddition Concentration Dependence (**79**).

compound	conc. (mM)	% yield 80 or 81
(*Z*)-**79**[a]	5	27–34
(*Z*)-**79**[a]	1	43
(*Z*)-**79**[a]	0.1	50
(*Z*)-**79**[a]	0.05	53
(*E*)-**79**[b]	100	38
(*E*)-**79**[b]	50	58
(*E*)-**79**[b]	10	86
(*E*)-**79**[b]	5	90
(*E*)-**79**[b]	1	99

[a] 230 °C, TIPB, 90 h.

[b] 230 °C, TIPB, 20 h.