Total Synthesis

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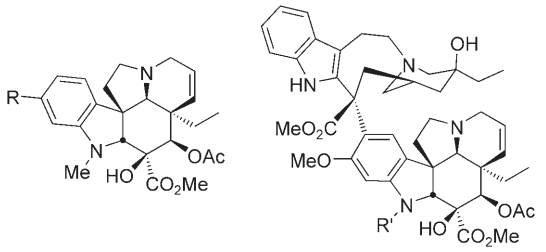
Total Synthesis of (−)- and *ent*-(+)-Vindorosine: Tandem Intramolecular Diels–Alder/1,3-Dipolar Cycloaddition of 1,3,4-Oxadiazoles**

*Gregory I. Elliott, Juraj Velcicky, Hayato Ishikawa, YongKai Li, and Dale L. Boger**

Vindorosine (**1**) is among the most complex, highly functionalized, and stereochemically rich natural products within a family of more than 90 alkaloids isolated from the Madagascan periwinkle (*Catharanthus roseus* (L.) G. Don).[1] The related C16-methoxy derivative vindoline (**2**) constitutes the

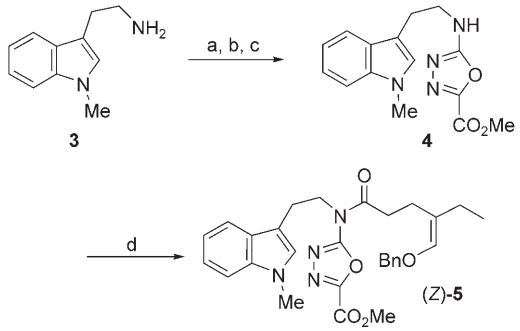


lower portion of vinblastine, which together with vincristine represent an important class of clinically effective anticancer therapeutics.[2]

As a consequence of its structural challenge and its relationship to vindoline, vindorosine has been the subject of a series of beautiful and historically important total syntheses.[3] In conjunction with our interest in developing an effective synthetic approach to vincristine and vinblastine, we report herein an unusually concise total synthesis of vindorosine developed as a prelude to efforts on vindoline[4] enlisting a tandem [4+2]/[3+2] cycloaddition cascade of 1,3,4-oxadiazoles. Limited reports of the cycloaddition reactions of electron-deficient and typically symmetrical 1,3,4-oxadiazoles have been detailed. In these studies, the groups of Vasilíev,[5] Sauer,[6] Seitz,[7] and most recently Warrener[8] have found that 1,3,4-oxadiazoles behave as electron-deficient azadienes and participate in intermolecular inverse-electron-demand Diels–Alder reactions to provide 2:1 cycloadducts with olefinic dienophiles.

The total synthesis of vindorosine (**1**) is based on a much more efficient intramolecular variant of the tandem [4+2]/[3+2] cycloaddition reaction that was inspired by the structures of the natural products.[9] The present reaction cascade is initiated by an intramolecular inverse-electron-demand Diels–Alder reaction of an electron-rich dienophile tethered to the 1,3,4-oxadiazole and is followed by the loss of N_2 and a subsequent intramolecular 1,3-dipolar cycloaddition of a tethered indole that proceeds with exclusive *endo* diastereoselectivity,[10] directed to the face of the 1,3-dipole opposite the fused lactam. This cycloaddition cascade not only produces the pentacyclic skeleton of **1** and introduces all the requisite substituents and functionality, but it also sets each of the six stereocenters found in vindorosine in a single step. As such, the 1,3,4-oxadiazole cycloaddition cascade, which introduces three new rings and four C–C bonds as well as all six key stereocenters, is ideally suited for the preparation of this class of natural products.

The requisite *N*-alkyl-2-amino-1,3,4-oxadiazole **4** was prepared in three steps (Scheme 1) from *N*-methyltryptamine (**3**).[9c] Thus, after treatment of **3** with CDI, the resulting



Scheme 1. Reagents and conditions: a) CDI, THF/CH_2Cl_2, 23 °C, 89%; b) methyl oxalylhydrazide, AcOH, THF, 40 °C, 93%; c) TsCl, Et_3N, CH_2Cl_2, 23 °C, 83%; d) (*Z*)-5-benzyloxy-4-ethylpent-4-enoic acid, EDCI, DMAP, CH_2Cl_2, 0–23 °C, 96%. Bn = benzyl, CDI = 1,1-carbonyldiimidazole, Ts = *p*-toluenesulfonyl, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide, DMAP = 4-(dimethylamino)pyridine.

imidazole urea (89%) was combined with methyl oxalylhydrazide to give the semicarbazide (93%), which was dehydrated to oxadiazole **4** (83%) by treatment with *p*-toluenesulfonyl chloride and triethylamine in CH_2Cl_2.[9c] Oxadiazole **4** was coupled with (*Z*)-5-benzyloxy-4-ethylpent-4-enoic acid to provide (*Z*)-**5** (96%), the precursor for the cycloaddition.

The cyclization of (*Z*)-**5** occurs in excellent yield when warmed in triisopropylbenzene for 60 h (Figure 1) to afford cycloadduct **6a** (78%) as a single detectable diastereomer. Initial attempts to cyclize (*Z*)-**5** provided **6a** in low yield (< 30% at > 5 mM), which is in contrast to the cyclization of the corresponding *E* isomer, (*E*)-**5**, which provides the C4 diastereomer **6b** in 86%.[9a] However, simple dilution of the reaction mixture led to improved yields (up to 78%). The results of a study of this unusual concentration effect are illustrated in Figure 1 and Table 1. A rather dramatic

[*] Dr. G. I. Elliott, Dr. J. Velcicky, Dr. H. Ishikawa, Dr. Y. Li, Prof. D. L. Boger
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-7550
E-mail: boger@scripps.edu

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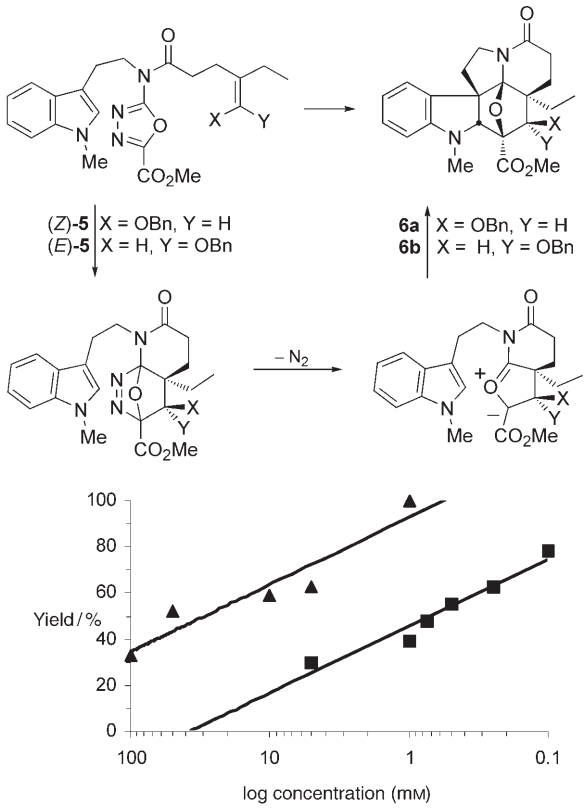


Figure 1. Concentration dependence of the yield of cycloaddition for the (*E*)-**5** (▲) and (*Z*)-**5** (■) in TIPB.

relationship between concentration and yield is observed, and this effect is most pronounced with (*Z*)-**5** which suggests that a competitive bimolecular reaction of **5** may compete with the intramolecular cycloaddition cascade at the higher reaction concentrations.

The enantiomers of cycloadduct **6a** proved readily separable by chiral-phase chromatography (semipreparative ChiralCel OD column, $2 \times 25\,cm^2$, 20% *i*PrOH in hexane, $10\,mL\,min^{-1}$, $t_R = 15.2$ and 21.3 min, $\alpha = 1.40$), which provided access to either enantiomer on a preparatively useful scale (150 mg/injection). α-Hydroxylation of cycloadduct **6a** was achieved by treatment of the lactam enolate with $(TMSO)_2$ and was followed by a direct quench of the reaction with TIPSOTf to provide silyl ether **7** in 60%. The α-hydroxylation reaction proceeded in a diastereoselective manner to provide **7** as a single diastereomer bearing an equatorial alcohol substituent (H7; dd, $J =$ 12.3, 6.2 Hz) as a result of the approach of the electrophile from the least-hindered convex face of the enolate. The amide **7** was converted into thioamide **8** (93%) with Lawesson's reagent.[11] Reduction of the thioamide with Raney nickel[10] occurred cleanly in 2 h, but the reaction was allowed to proceed longer (16 h), leading to subsequent cleavage of the benzyl ether to provide the alcohol **9** (80%) directly in a single step (Scheme 2, only the natural enantiomer is shown).

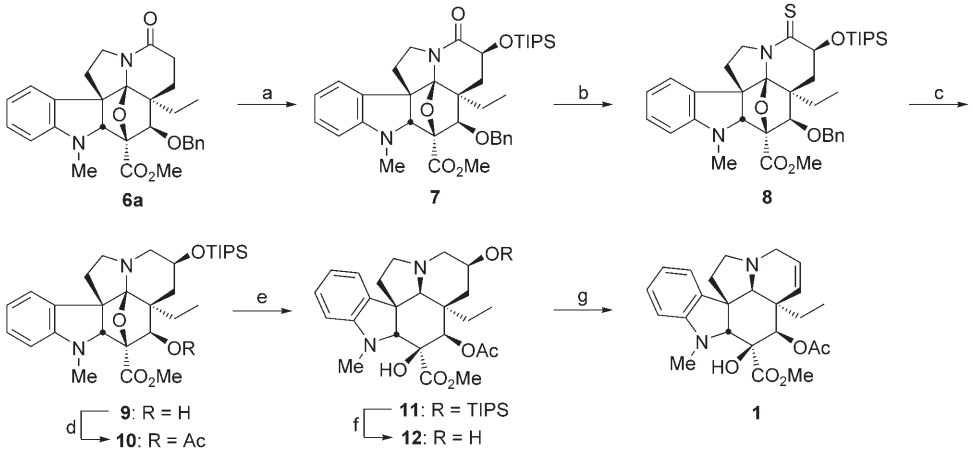
Table 1: Concentration dependence of the yield of cycloaddition.

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

[a] Conditions: 230°C, TIPB, 60 h. [b] Conditions: 180°C, *o*-DCB, 24 h. [c] Preparative scale, multiple runs. [d] Conditions: 230°C, TIPB, 18 h. TIPB = 1,3,5-triisopropylbenzene, *o*-DCB = *o*-dichlorobenzene.

Acetylation of secondary alcohol **9** with acetic anhydride (97%), followed by a diastereoselective reductive opening of the oxido bridge of **10** (93%, H_2/PtO_2),[10] and subsequent deprotection of the TIPS ether **11** with Bu_4NF afforded diol **12** (99%). A final regioselective elimination of the secondary alcohol **12** using Ph_3P/DEAD provided vindorosine (**1**, 74%), which was identical in all comparable respects with properties reported for the natural material.

In conclusion, an unusually concise total synthesis of the vinca alkaloid vindorosine has been developed. The key step in the synthesis is a highly efficient and diastereoselective intramolecular tandem [4+2]/[3+2] cycloaddition reaction of 1,3,4-oxadiazole that allows direct access to the pentacyclic aspidosperma skeleton in a reaction cascade that not only



Scheme 2. Reagents and conditions: a) 1. LDA, $(TMSO)_2$, THF −40°C; 2. TIPSOTf, iPr_2NEt, 23°C, 60%; b) Lawesson's reagent, toluene, 100°C, 93%; c) Raney Ni, H_2, THF, 23°C, 80%; d) Ac_2O, NaOAc, 23°C, 97%; e) PtO_2, H_2 (40 psi), MeOH/EtOAc (1:1), 23°C, 93%; f) Bu_4NF, THF, 0–23°C, 99%; g) Ph_3P/DEAD, THF, 23°C, 74%. LDA = lithium diisopropylamide, TMS = trimethylsilyl, TIPS = triisopropylsilyl, OTf = trifluoromethanesulfonate, DEAD = diethyl azodicarboxylate.

results in the formation of four new C–C bonds and three rings but also introduces all of the requisite functionality and all six stereocenters about the central six-membered ring of the natural product in a single reaction. Further development of the oxadiazole cascade cycloaddition reactions and their potential applications will be reported in due course.

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