ORGANIC LETTERS

2005
Vol. 7, No. 4
741−744

Total Synthesis of Natural (−)- and *ent*-(+)-4-Desacetoxy-6,7-dihydrovindorosine and Natural and *ent*-Minovine: Oxadiazole Tandem Intramolecular Diels−Alder/1,3-Dipolar Cycloaddition Reaction

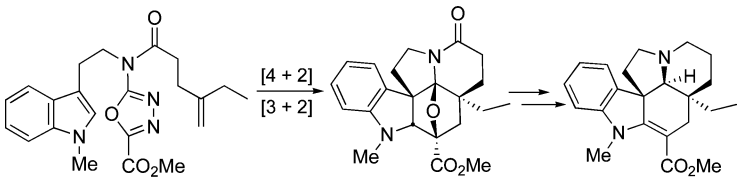
Zhong Qing Yuan, Hayato Ishikawa, and Dale L. Boger*

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

boger@scripps.edu

Received January 5, 2005

ABSTRACT



9 **10** **Minovine (1)**

Efficient and unusually concise total syntheses of both enantiomers of the Aspidosperma alkaloids 4-desacetoxy-6,7-dihydrovindorosine (12) and minovine (1) are detailed. A tandem intramolecular Diels−Alder/1,3-dipolar cycloaddition reaction of the 1,3,4-oxadiazole 8, in which three new rings, four new C−C bonds, and five stereocenters are formed, is a key step in the sequence. The availability of optically active material permitted an assessment of the enantiomeric integrity of minovine and the source of its reported unusual optical rotation.

Minovine (**1**),[1] a naturally occurring Aspidosperma alkaloid isolated from *Vinca minor L.*, bears the pentacyclic vincadifformine skeleton. Due to its inherent structural complexity and pentacyclic skeleton characteristic of the Aspidosperma alkaloids, minovine has attracted considerable synthetic interest throughout the years.[2] We describe herein a concise total synthesis of minovine and 4-desacetoxy-6,7-dihydrovindorosine enlisting a novel tandem intramolecular Diels−Alder/1,3-dipolar cycloaddition cascade of a suitably substituted 2-amino-1,3,4-oxadiazole.

Only a limited number of reports have described the cycloaddition of electron-deficient 1,3,4-oxadiazoles, and they typically employ symmetrical oxadiazoles bearing strong electron-withdrawing substituents (CF_3, SO_2Et, CO_2Me) in intermolecular reactions.[3] Reactions with olefinic dienophiles have been shown to proceed through an initial [4 + 2] cycloadduct that subsequently loses N_2 to generate a carbonyl ylide, which reacts further with the olefin in a 1,3-dipolar cycloaddition. In recent efforts, we have extended the scope of this reaction beyond that which provides symmetrical 2:1 cycloadducts by implementing the reaction cascade in an

(1) Mokry, J.; Dubravkova, L.; Sefcovic, P. *Experientia* **1962**, *18*, 564−565. Mokry, J.; Kompis, I.; Dubravkova, L.; Sefcovic, P. *Experientia* **1963**, *19*, 311. Zachystalova, D.; Strouf, O.; Trojanek, J. *Chem. Ind.* **1963**, *13*, 610−611.

(2) Kutney, J. P.; Chan, K. K.; Failli, A.; Fromson, J. M.; Gletsos, C.; Leutwiler, A.; Nelson, V. R. *J. Am. Chem. Soc.* **1968**, *90*, 3891−3893. Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146−7149. Kutney, J. P.; Chan, K. K.; Failli, A.; Fromson, J. M.; Gletsos, C.; Leutwiler, A.; Nelson, V. R.; de Souza, J. P. *Helv. Chim. Acta* **1975**, *58*, 1648−1671. Kuehne, M. E.; Huebner, J. A.; Matsko, T. H. *J. Org. Chem.* **1979**, *44*, 2477−2480. Kalaus, G.; Kiss, M.; Kajtar-Peredy, M.; Brlik, J.; Szabo, L.; Szantay, C. *Heterocycles* **1985**, *23*, 2783−2787.

10.1021/ol050017s CCC: $30.25
Published on Web 01/25/2005

intramolecular fashion.[4] In the cases examined, olefinic dienophiles tethered to a 2-amino-1,3,4-oxadiazole react to form the initial [4 + 2] cycloadduct that loses N_2 to generate a carbonyl ylide that was trapped by a tethered indole (Figure 1). The relative stereochemistry is set by a combination of

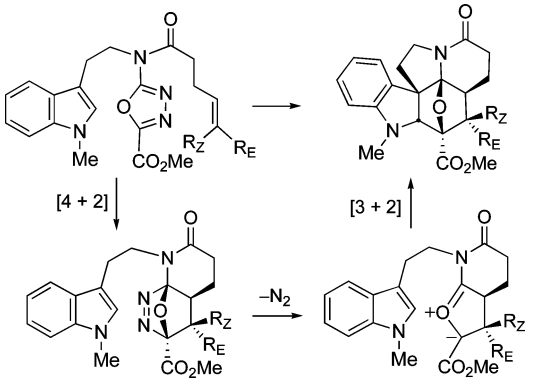
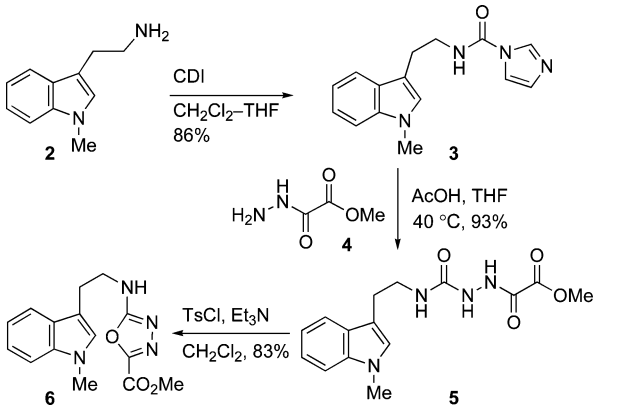


Figure 1. Tandem intramolecular [4 + 2]/[3 + 2] cycloaddition reactions of a 1,3,4-oxadiazole.

the dienophile geometry and the exclusive indole endo [3 + 2] cycloaddition sterically directed to the face opposite the fused lactam. Impressively, the tandem cycloadditions construct three new rings with formation of four new C−C bonds and set all six stereocenters about the central six-membered ring in a single step without a trace of a second diastereomer. Herein, we describe the application of this cycloaddition cascade to the total synthesis of minovine and 4-desacetoxy-6,7-dihydrovindorosine.

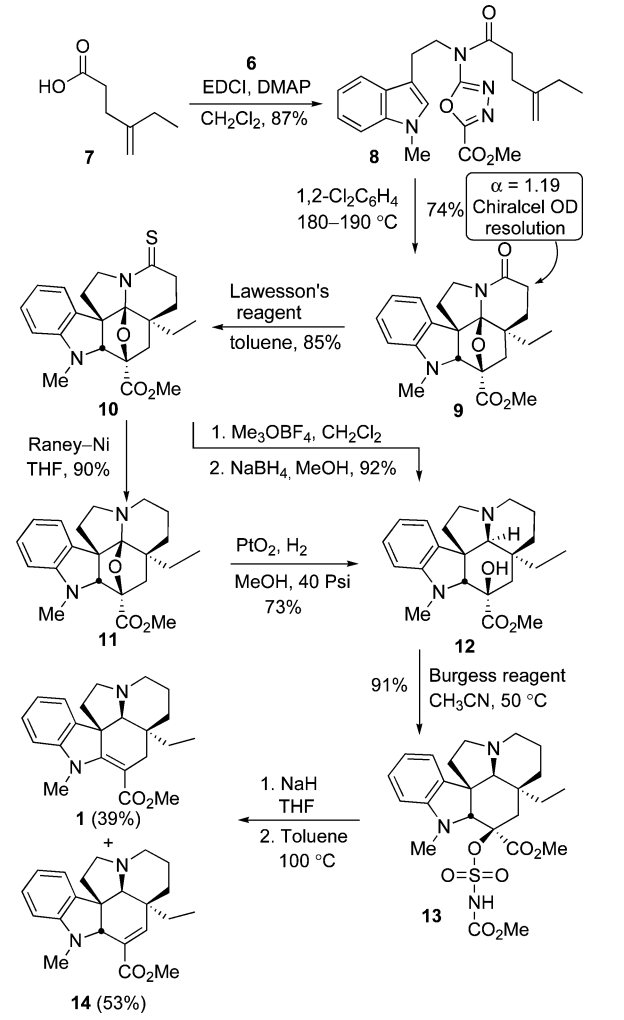
The starting 2-amino-1,3,4-oxadiazole **6** was prepared from *N*-methyl tryptamine (**2**, Scheme 1). Treatment of **2** with carbonyldiimidazole afforded **3** (86%), which was converted to the oxadiazole precursor **5** (93%) by treatment with methyl oxalylhydrazide (**4**)[5] in the presence of HOAc. Cyclization of **5** to form the corresponding oxadiazole **6** was mediated by TsCl and Et_3N (83%).

Scheme 1. Preparation of 1,3,4-Oxadiazole **6**



Coupling of **6** with 4-ethyl-4-pentenoic acid (**7**)[6] was effected by EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimidide hydrochloride) and DMAP to provide the substrate **8** (87%) for the key [4 + 2]/[3 + 2] cycloaddition cascade (Scheme 2). The tandem intramolecular cycloaddi-

Scheme 2. Synthesis of 4-Desacetoxy-6,7-dihydrovindorosine and Minovine



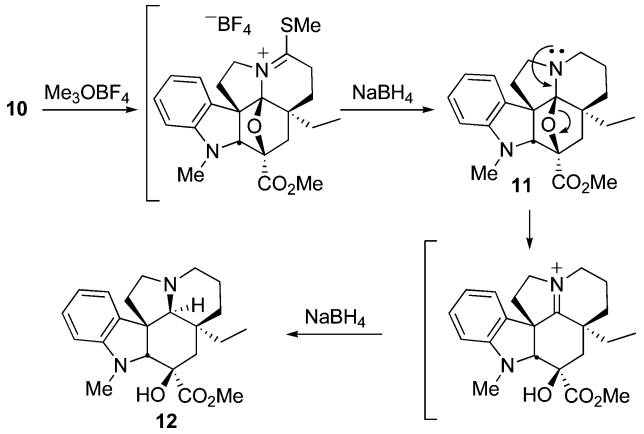
(3) Vasiliev, N. V.; Lyashenko, Y. E.; Kolomiets, A. F.; Sokolskii, G. A. *Khim. Geterotsikl. Soedin.* **1987**, 562. Vasiliev, N. V.; Lyashenko, Y. E.; Galakhov, M. V.; Kolomiets, A. F.; Gontar, A. F.; Sokolskii, G. A. *Khim. Geterotsikl. Soedin.* **1990**, 95−100. Vasiliev, N. V.; Lyashenko, Y. E.; Patalakha, A. E.; Sokolskii, G. A. *J. Fluorine Chem.* **1993**, *65*, 227−231. Thalhammer, F.; Wallfahrer, U.; Sauer, J. *Tetrahedron Lett.* **1988**, *29*, 3231−3234. Seitz, G.; Gerninghaus, C. H. *Pharmazie* **1994**, *49*, 102−106. Seitz, G.; Wassmuth, H. *Chem.-Ztg.* **1988**, *112*, 80−81. Review: Warrener, R. N. *Eur. J. Org. Chem.* **2000**, 3363−3380. Warrener, R. N.; Margetic, D.; Foley, P. J.; Butler, D. N.; Winling, A.; Beales, K. A.; Russell, R. A. *Tetrahedron* **2001**, *57*, 571−582. Warrener, R. N.; Wang, S.; Maksimovic, L.; Tepperman, P. M.; Butler, D. N. *Tetrahedron Lett.* **1995**, *36*, 6141−6144. Warrener, R. N.; Elsey, G. M.; Russell, R. A.; Tiekink, E. R. T. *Tetrahedron Lett.* **1995**, *36*, 5275−5278. Warrener, R. N.; Maksimovic, L.; Butler, D. N. *J. Chem. Soc., Chem. Commun.* **1994**, 1831−1888. Warrener, R. N.; Butler, D. N.; Liao, W. Y.; Pitt, I. G.; Butler, D. N.; Russell, R. A. *Tetrahedron Lett.* **1991**, *32*, 1885−1888. Warrener, R. N.; Margetic, D.; Tiekink, E. R. T.; Russell, R. A. *Synlett* **1997**, 196−198.

(4) Wilkie, G. D.; Elliott, G. I.; Blagg, B. S. J.; Wolkenberg, S. E.; Soenen, D. R.; Miller, M. M.; Pollack, S.; Boger, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 11292−11294. Wolkenberg, S. E.; Boger, D. L. *J. Org. Chem.* **2002**, *67*, 7361−7364.

(5) Christl, M.; Lanzendoerfer, U.; Groetsch, M. M.; Ditterich, E.; Hegmann, J. *Chem. Ber.* **1990**, *123*, 2031−2037.

tion reaction proceeded in excellent yield (74%) upon warming a solution of **8** at 180 °C in *o*-diclorobenzene for 24 h to provide **9** as a single detectable diastereomer possessing the Aspidosperma alkaloid pentacyclic skeleton (natural enantiomer depicted). Treatment of cycloadduct **9** with Lawesson's reagent[7] furnished thiolactam **10** in 85% yield. Desulfurization and opening of the oxido bridge was initially effected by reduction of **10** with Raney-Ni to provide **11** (90%) followed by reductive oxido bridge cleavage by PtO_2-catalyzed hydrogenation[8] providing 4-desacetoxy-6,7-dihydrovindorosine (**12**, 73%).[9] Alternatively, S-methylation of the thiolactam **10** with Me_3OBF_4 followed by $NaBH_4$ reduction[10] in MeOH directly provided 4-desacetoxy-6,7-dihydrovindorosine (**12**) in superb yield (92%) as a single operation sequence (Scheme 3). The relative stereochemistry

Scheme 3. Desulfurization and Reductive Oxido-Bridge Opening



in **12** was first established by observation of diagnostic ^{1}H−^{1}H ROSEY NOEs between the C5 ethyl and C19 protons and was confirmed with a single-crystal X-ray structure of **12** (Figure 2).[11] Treatment of **12** with the Burgess reagent[12] in CH_3CN first provided the sulfamate **13** (91%) which upon isolation and heating in toluene at 100 °C in the presence of NaH furnished minovine (**1**) and its isomer **14**. Although not investigated in detail, attempts to promote a direct single pot dehydration of **12** to provide **1** with the Burgess reagent were not successful, analogous initial efforts to utilize Martin's sulfurane[13] were not successful, and no effort was made to alter or optimize the isomeric ratio of **1** and **14**.[14]

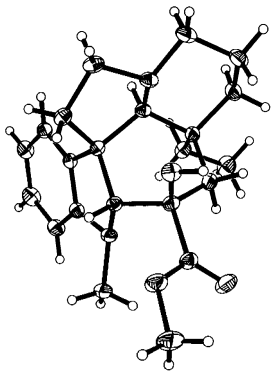
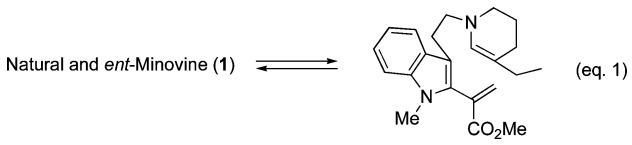


Figure 2. X-ray ORTEP of **12**.

Naturally occurring minovine (**1**) has been reported only with an $[\alpha]_D = 0$ in alcoholic solvents.[1] This raised the question of whether the rotation of **1** was simply 0 or whether natural minovine might suffer from a facile racemization. This latter racemization could be envisioned to occur simply by retro [4 + 2] cycloaddition of **1**, providing an achiral intermediate lacking any stereocenters, followed by a diastereoselective but not enantioselective [4 + 2] cycloaddition, eq 1. Consequently, the synthesis of **1** and **14** was repeated



with optically active material obtained by chromatographic resolution of **9**. Thus, separation of the enantiomers of **9** ($\alpha = 1.19$, 20 mg/injection) was carried out on a semipreparative Daicel Chiralcel OD column (2 cm × 25 cm, 10% *i*-PrOH/hexane, 10 mL/min flow rate) providing natural-(+)-**9** (t_R = 31.7 min) and *ent*-(−)-**9** (t_R = 26.7 min) which were converted to natural-(−)-**14** ($[\alpha]^{23}_D$ −145 (*c* 0.33, $CHCl_3$), $[\alpha]^{23}_D$ −122 (*c* 0.67, MeOH)) and *ent*-(+)-**14** ($[\alpha]^{23}_D$ +143 (*c* 0.90, $CHCl_3$), $[\alpha]^{23}_D$ +126 (*c* 0.83, MeOH)) and natural and *ent*-**1**. The natural enantiomer series was assigned on the basis of comparison with **12**[9], which has been independently prepared in optically active form in prior studies. Minovine exhibited a remarkable solvent-dependent but concentration-independent range of optical rotations: natural **1** $[\alpha]^{23}_D$ −17 (*c* 0.35, $CHCl_3$), +16 (*c* 0.40, MeOH), and 0 ±3 (*c* 0.28, EtOH). Moreover, the enantiomeric integrity of **1** was maintained not only upon storage but also upon deliberate attempts to promote racemization via the potentially reversible Diels−Alder reaction illustrated in eq 1. Thus, warming **1** in MeOH (80 °C, 24−48 h), toluene (120

(6) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137−2139. Reinheckel, H.; Sonnek, G.; Gensike, R. *J. Prakt. Chem.* **1975**, *317*, 273−283. McCaffery, E. L.; Shalaby, S. W. *J. Organomet. Chem.* **1967**, *8*, 17−27.

(7) Yde, B.; Yousif, N. M.; Pedersen, U.; Thomsen, I.; Lawesson, S. O. *Tetrahedron* **1984**, *40*, 2047−2052.

(8) Padwa, A.; Price, A. T. *J. Org. Chem.* **1998**, *63*, 556−565.

(9) Enantiomerically pure **12** has been reported: Calabi, L.; Danieli, B.; Lesma, G.; Palmisano, G. *J. Chem. Soc., Perkin Trans. I* **1982**, 1371−1379. Hugel, G.; Levy, J. *Tetrahedron* **1984**, *40*, 1067−1073.

(10) Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, *21*, 4061−4064.

(11) Atomic coordinates for **12** have been deposited with Cambridge Crystallographic Data Center under the deposition number CCDC 231165.

(12) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26−31. Lamberth, C. *J. Prakt. Chem.* **2000**, *342*, 518−522.

(13) Arhart, R. J.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5003−5010. Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327−4329. Box, J. M.; Harwood, L. M.; Humphreys, J. L.; Morris, G. A.; Redon, P. M.; Whitehead, R. C. *Synlett* **2002**, 358−360.

(14) This reaction proceeds in part by aziridinium formation via intramolecular sulfamate displacement favoring formation of **14**.

°C, 21 h), or DMF (80, 120, or 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 **1** were readily separable (t_R = 10.0 min (natural **1**) and 8.29 min (*ent*-**1**), Chiralcel OD 0.46 cm × 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 (EtOH) as reported,[1] but this is not because it is racemic.

Thus, an unusually concise and convergent total synthesis of both enantiomers of 4-desacetoxy-6,7-dihydrovindorosine and minovine was developed enlisting a tandem intramolecular Diels−Alder/1,3-dipolar cycloaddition cascade of a suitably substituted 1,3,4-oxadiazole. The availability of optically active material permitted an assessment of the enantiomeric integrity of minovine and the source of its reported unusual optical rotation. Further studies of the scope of such reactions and their applications are in progress and will be reported in due course.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA42056) and thank Dr. R. Chadha for the X-ray structure determination of **12**.

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

OL050017S