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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

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Abstract

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 (CF₃, SO₂Et, CO₂Me) in intermolecular reactions.³ Reactions with olefinic dienophiles have been shown to proceed through an initial [4 + 2] cycloadduct that subsequently loses N₂ 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 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 N₂ to generate a carbonyl ylide which was trapped by a tethered indole (Figure 1). The relative stereochemistry is set by a combination of 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.

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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 Et₃N (83%).

Coupling of **6** with 4-ethyl-4-pentenoic acid (**7**)⁶ was effected by EDCI (1-[3-(dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride) and DMAP to provide the substrate **8** (87%) for the key [4 + 2]/[3 + 2] cycloaddition cascade (Scheme 2). The tandem intramolecular cycloaddition reaction proceeded in excellent yield (74%) upon warming a solution of **8** at 180 °C in *o*-dichlorobenzene 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 reagent⁷ 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 PtO₂-catalyzed hydrogenation⁸ providing 4-desacetoxy-6,7-dihydrovindorosine (**12**, 73%).⁹ Alternatively, *S*-methylation of the thiolactam **10** with Me₃OBf₄ followed by NaBH₄ reduction¹⁰ in MeOH directly provided 4-desacetoxy-6,7-dihydrovindorosine (**12**) in superb yield (92%) as a single operation sequence (Scheme 3). The relative stereochemistry in **12** was first established by observation of diagnostic ¹H-¹H ROSEY nOe's 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 reagent¹² in CH₃CN 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 sulfurane¹³ were not successful, and no effort was made to alter or optimize the isomeric ratio of **1** and **14**.¹⁴

Naturally occurring minovine (**1**) has been reported only with an [α]_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** (α = 1.19, 20 mg/injection) was carried out on a semipreparative Daicel Chiralcel OD column (2 × 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** ([α]_D²³ -145 (c 0.33, CHCl₃), [α]_D²³ -122 (c 0.67, MeOH)) and *ent*-(+)-**14** ([α]_D²³ +143 (c 0.90, CHCl₃), [α]_D²³ +126 (c 0.83, MeOH)) and natural and *ent*-**1**. The natural enantiomer series was assigned based on 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** [α]_D²³ -17 (c 0.35, CHCl₃), +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 equation 1. Thus, warming **1** in MeOH (80 °C, 24–48 h), toluene (120 °C, 21 h), or DMF (80 °C, 120 °C 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 × 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.

(eq. 1)

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Mokry J, Dubravkova L, Sefcovic P. *Experientia* 1962;18:564–565. [PubMed: 13935802] Mokry J, Kompis I, Dubravkova L, Sefcovic P. *Experientia* 1963;19:311. [PubMed: 13935801] Zachystalova D, Strouf O, Trojanek J. *Chem Industry* 1963;13:610–611.
2. Kutney JP, Chan KK, Failli A, Fromson JM, Gletsos C, Leutwiler A, Nelson VR. *J Am Chem Soc* 1968;90:3891–3893. [PubMed: 5653833] Ziegler FE, Spitzner EB. *J Am Chem Soc* 1973;95:7146–7149. [PubMed: 4784289] Kutney JP, Chan KK, Failli A, Fromson JM, Gletsos C, Leutwiler A, Nelson VR, de Souza JP. *Helv Chim Acta* 1975;58:1648–1671. [PubMed: 1176298] Kuehne ME, Huebner JA, Matsko TH. *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.
3. Vasiliev NV, Lyashenko YE, Kolomiets AF, Sokolskii GA. *Khim Geterotsikl Soedin* 1987;562. Vasiliev NV, Lyashenko YE, Galakhov MV, Kolomiets AF, Gontar AF, Sokolskii GA. *Khim Geterotsikl Soedin* 1990;95–100. Vasiliev NV, Lyashenko YE, Patalakha AE, Sokolskii GA. *J Fluorine Chem* 1993;65:227–231. Thalhammer F, Wallfahner U, Sauer J. *Tetrahedron Lett* 1988;29:3231–3234. Seitz G, Gerninghaus CH. *Pharmazie* 1994;49:102–106. Seitz G, Wassmuth H. *Chem -Ztg* 1988;112:80–81. Review: Warrenner RN. *Eur J Org Chem* 2000;3363–3380. Warrenner RN, Margetic D, Foley PJ, Butler DN, Winling A, Beales KA, Russell RA. *Tetrahedron* 2001;57:571–582. Warrenner RN, Wang S, Maksimovic L, Tepperman PM, Butler DN. *Tetrahedron Lett* 1995;36:6141–6144. Warrenner RN, Elseby GM, Russell RA, Tiekink ERT. *Tetrahedron Lett* 1995;36:5275–5278. Warrenner RN, Maksimovic L, Butler DN. *J Chem Soc Chem Commun* 1994:1831–1888. Warrenner RN, Butler DN, Liao WY, Pitt IG, Butler DN, Russell RA. *Tetrahedron Lett* 1991;32:1885–1888. Warrenner RN, Margetic D, Tiekink ERT, Russell RA. *Synlett* 1997:196–198.
4. Wilkie GD, Elliott GI, Blagg BSJ, Wolkenberg SE, Soenen DR, Miller MM, Pollack S, Boger DL. *J Am Chem Soc* 2002;124:11292–11294. [PubMed: 12236743] Wolkenberg SE, Boger DL. *J Org Chem* 2002;67:7361–7364. [PubMed: 12375965]
5. Christl M, Lanzendoerfer U, Groetsch MM, Ditterich E, Hegmann J. *Chem Ber* 1990;123:2031–2037.
6. Yokoshima S, Ueda T, Kobayashi S, Sato A, Kuboyama T, Tokuyama H, Fukuyama T. *J Am Chem Soc* 2002;124:2137–2139. [PubMed: 11878966] Reinheckel H, Sonnek G, Gensike R. *J Prakt Chem* 1975;317:273–283. McCaffery EL, Shalaby SW. *J Organomet Chem* 1967;8:17–27.

7. Yde B, Yousif NM, Pedersen U, Thomsen I, Lawesson SO. *Tetrahedron* 1984;40:2047–2052.
8. Padwa A, Price AT. *J Org Chem* 1998;63:556–565. [PubMed: 11672045]
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 EM, Penton HR Jr, Taylor EA. *J Org Chem* 1973;38:26–31. Lamberth C. *J Prak Chem* 2000;342:518–522.
13. Arhart RJ, Martin JC. *J Am Chem Soc* 1972;94:5003–5010. Martin JC, Arhart RJ. *J Am Chem Soc* 1971;93:4327–4329. Box JM, Harwood LM, Humphreys JL, Morris GA, Redon PM, Whitehead RC. *Synlett* 2002:358–360.
14. This reaction proceeds in part by aziridinium formation via intramolecular sulfamate displacement favoring formation of **14**.

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

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

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

Scheme 2.
 Synthesis of 4-desacetoxy-6,7-dihydrovindorosine and minovine

Scheme 3.
Desulfurization and reductive oxido-bridge opening