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First total synthesis of (+)-Vedelianin, a potent antiproliferative agent

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Abstract

The total synthesis of (+)-vedelianin has been accomplished in 18 steps from vanillin. Preparation of a key intermediate in nonracemic form through a Shi epoxidation has allowed determination of the absolute stereochemistry of the natural product as the (2*S*, 3*R*, 4*aR*, 9*aR*)-isomer.

In 1992, the structure of vedelianin (**1**) was reported as part of an ethno-pharmacological investigation seeking compounds with hypotensive activity in extracts of *Macaranga vedeliana*.¹ Although no such activity was noted for this compound, subsequent studies led to the first recognition of its potent antiproliferative activity,² and a later investigation of a related plant led to isolation of vedelianin from *M. alnifolia*.³ Of the compounds isolated from *M. alnifolia*, vedelianin was found to be the most potent antiproliferative agent in one assay (IC₅₀ = 130 nM vs. A2780 cells),³ and it also has been found to have a mean GI₅₀ of 78 nM in the 60 cell line assay of the National Cancer Institute (NCI).^{2,4} and several individual cell lines have shown GI₅₀ values below 1 nM. Based on vedelianin's similarity to the natural schweinfurthins⁴ (e.g. schweinfurthin A, **2**), its intriguing profile of activity in the NCI assays, and our interest in schweinfurthin synthesis,⁵ we undertook a total synthesis of vedelianin so that this potent member of the natural family would be accessible for further biological evaluation.

The total synthesis of vedelianin began with the known benzyl alcohol **4**, which is available in four steps and ~50% overall yield from vanillin (**3**, Scheme 1).^{5a,5g} Methylation of this intermediate via a Williamson ether synthesis then provided methyl ether **5** in excellent yield. Exposure of compound **5** to *n*-BuLi resulted in halogen–metal exchange, and when the resulting anion was quenched by slow addition of geranyl bromide the alkylated arene **6** was obtained.⁶ Epoxidation of the terminal olefin under Shi's conditions⁷ proceeded to afford nonracemic epoxide **7** in high enantiomeric excess (average ee of 89% by HPLC analysis).^{5f} Higher regio- and enantioselectivity could be obtained if the epoxidation was quenched prior to complete conversion, which resulted in quantities of recyclable starting material.

In our past work it has been shown that an ortho MOM group can be used to terminate a cascade cyclization,^{5g} although the liberated MOM group sometimes is found as part of a C-2 acetal. In this case, when epoxide **7** was treated with BF₃·OEt₂ the epoxide-initiated

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Supplementary data

Experimental procedures and/or spectral data for compounds **1**, **5-11**, **13-17**, and **19** are available. Supplementary data associated with this article can be found, in the online version, at doi:

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cascade cyclization proceeded smoothly to provide a roughly 2:1 mixture of hexahydroxanthenes **8** and **9**, and each product was obtained as a single isomer. All observations support the conclusion that this cascade process proceeds with complete diastereoselectivity to afford the trans-fused products shown.^{5g} Compounds **8** and **9** can be interconverted readily, either through protection of the A- ring hydroxyl group of compound **8** or hydrolysis of both MOM groups of compound **9** and selective protection of the C-ring phenol. This makes both compounds useful intermediates and increases material throughput for vedelianin. Alternatively, oxidation of the individual benzyl methyl ethers **8** and **9** upon exposure to DDQ^{8,5h} provided aldehydes **10** and **11** respectively, and excellent yields were obtained in each case. The synthesis of compound **10** constitutes a formal synthesis of the closely related, although less potent, natural product schweinfurthin G.^{3, 5g}

A vedelianin synthesis required elaboration of the hexahydroxanthene **8** to an A-ring diol (Scheme 2). Incorporation of a latent carbonyl group at the C-3 position was accomplished through a known three-step sequence first applied to prepare a related system.^{5h,5l} Thus compound **8** was oxidized to the corresponding ketone by treatment with TPAP and NMNO, condensed with benzaldehyde in the presence of potassium hydroxide through a classic Claisen condensation, and reduced cleanly to the allylic alcohol **12** under Luche conditions.^{5l,9} In this series, protection of alcohol **12** was necessary to allow direct oxidative cleavage of the olefin with KMnO₄, unmasking the latent C-3 ketone without oxidation at C-2. Therefore, alcohol **12** was treated with MOMCl and base to yield acetal **13**. While use of this protecting group introduces an additional step to the synthetic sequence, this reaction proceeds in nearly quantitative yield when conducted at high concentrations and the C-2 MOM group can be removed as part of a late stage, global deprotection strategy. Treatment of the MOM acetal **13** with excess KMnO₄ resulted in direct formation of ketone **14**. This ketone could be reduced with complete selectivity to afford alcohol **15** as a single product.¹⁰ In this compound, the ¹H NMR resonance for the C-3 hydrogen displayed coupling constants in good agreement with vedelianin (an apparent quartet with a *J* of ~3.2 Hz), and matches what would be expected for an equatorial hydrogen. Application of the DDQ-based oxidative deprotection then gave aldehyde **16** in quantitative yield.

With aldehyde **16** in hand, the conclusion of vedelianin's synthesis appeared to be straightforward, and the necessary HWE condensation first was attempted with phosphonate **18** under standard conditions^{5d,5k} without protection of the C-3 hydroxyl group. However, when aldehyde **16** was treated with excess NaH and phosphonate **18**^{5e} only trace amounts of the desired stillbene were isolated, and brief exploration of other conditions lead to only a marginal improvement in yield. This was somewhat surprising given that similar HWE condensations in the 3-deoxy series routinely have been conducted without protection of the C-2 hydroxyl group. The sensitivity of compound **16** to strong base may result from a competing Grob fragmentation.^{11,12} While constraints imposed on this system by the planarity of the C-ring may make it difficult to achieve an ideal conformation for a concerted Grob fragmentation, the Bring oxygen does provide a good leaving group in the form of a phenoxide and a variety of non-concerted mechanisms are recognized.¹² To minimize the possibility of a base-induced fragmentation, it was decided to protect the C-3 hydroxyl group. Treatment of aldehyde **16** with excess MOMCl and diisopropylethylamine resulted in quantitative formation of acetal **17**. When the HWE condensation was attempted with the fully protected aldehyde **17** and KHMDS as base, olefination was facile and stilbene **19** was isolated in good yield. Stilbene **19** was treated with TsOH in methanol, resulting in hydrolysis of all five MOM acetal groups to afford vedelianin (**1**) along with a significant amount of partially hydrolyzed materials.¹³ The ¹H and ¹³C NMR spectra of the synthetic vedelianin are in excellent agreement with those reported for the natural product.¹ Furthermore, the specific rotation of the synthetic material matched both the sign and magnitude reported for vedelianin (lit¹ +37, observed +35.3, for material of 90% ee by

HPLC), which indicates that compound **1** has been prepared as the naturally occurring antipode. Based on the known absolute stereochemistry of aldehyde **10**,^{5g} ultimately generated by Shi epoxidation, the absolute stereochemistry of (+)-vedelianin now can be assigned as the (2*S*, 3*R*, 4*aR*, 9*aR*)-isomer.

In conclusion, we have accomplished the first total synthesis of (+)-vedelianin in 18 steps from vanillin. In addition, this work represents a more direct synthesis of the related compound schweinfurthin G. Finally, aldehydes **10**, **11**, **16**, and **17** can serve as key intermediates in further efforts to delineate structure-activity relationships and in the synthesis of mechanistic probes to uncover vedelianin's unique, and as yet unidentified, mechanism of antiproliferative activity.

Supplementary Material

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Acknowledgments

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prepared by other means.^{5g} Single crystal diffraction analyses of both trans-fused^{5h} and cis-fused⁵ⁱ hexahydroxanthenes have confirmed that the stereochemistry of the epoxide controls the stereochemistry of the ring fusion in the tricyclic product.

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13. Hydrolysis of the C-2 and C-3 MOM groups proceeds significantly more slowly than hydrolysis of the phenolic MOM groups. Based on TLC analysis of the reaction mixture, we hypothesize that the partially hydrolyzed material is a mixture of vedelianin derivatives that still carry MOM groups at C-2 and/or C-3.

Figure 1.
Natural hexahydroxanthenes.

Scheme 1.

A formal synthesis of schweinfurthin G.

Scheme 2.
Total synthesis of vedelianin.