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Expedient Enantioselective Synthesis of Cermizine D

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Abstract

An efficient enantioselective synthesis of cermizine D has been developed that exploits the use of a common intermediate to access over 85% of the carbon backbone. Key steps include an organocatalyzed heteroatom Michael addition, a diastereoselective alkylation with α -iodomethyl phenyl sulfide, a conjugate addition to a vinyl sulfone species and a sulfone coupling / desulfurization sequence to join the two major subunits.

Cermizine D (**1**) was isolated in 2004 by Kobayashi and co-workers from the club moss *Lycopodium cernuum* and displaced modest cytotoxicity against murin lymphoma L1210 cells (7.5 $\mu\text{g} / \text{mL}$).¹ Related cermizine alkaloids have attracted the attention of several laboratories.² To date, one elegant eighteen-step total synthesis of **1** has been reported by Takayama and co-workers.³ Herein, we report an efficient, enantioselective synthesis of cermizine D, which exploits the use of a common intermediate strategy to access two of the three piperidine rings.

Our retrosynthetic strategy is shown in Scheme 1. We envision that the C₇-N bond could be formed through an intramolecular S_N²-type cyclization of alcohol **2**. Alcohol **2** would in turn be accessible from a sulfone-aldehyde coupling / desulfurization sequence using sulfone **3** and common intermediate **4**. Sulfone **3** would be accessible from the same common intermediate **4**.

The synthesis commenced with the commercially available amine **5** (Scheme 2). The amine can also be conveniently prepared from 1-bromo-5-hexene through a two-step sequence.⁴ Subsequent Boc protection gave the known alkene **6**.⁵ After cross-metathesis using crotonaldehyde, intramolecular heteroatom Michael addition (under a slight modification of

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Supporting Information Available Complete experimental procedures are provided, including ¹H and ¹³C spectra, of all new compounds. X-ray crystallographic data (CIF) for compound **15** is also provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

our previously reported conditions⁴) employing catalyst **9**⁶ cleanly generated the piperidine **4** in 85% yield and 96% ee as determined by chiral HPLC analysis.^{5,7}

Our first generation approach for the conversion of the common intermediate **4** into sulfone **3** is shown in Scheme 3. Homologation via Wittig olefination and enol ether cleavage revealed aldehyde **11**. Pinnick oxidation followed by coupling with Evans oxazolidinone **12** generated compound **13**. Diastereoselective alkylation⁸ was best achieved using NaHMDS as base to provide a good yield of methyl product **15** in modest diastereoselectivity (1.5:1 dr). The absolute stereochemistry of alkylation product **15** was determined by x-ray crystallographic analysis (Figure 1). The poor level of diastereoselectivity appears to be a result of a mis-matched stereochemical array in **13**; use of the diastereomeric oxazolidinone series **14** generated the alkylated product **17** in high levels of stereoselectivity (20:1 dr). Subsequent reductive removal of the oxazolidinone **15** followed by conversion to the sulfide and oxidation generated the sulfone **3**.

Given poor diastereoselectivity in constructing the C₁₅ stereogenic center, we sought an alternate approach (Scheme 4). We were intrigued by the possibility of exploiting the matched stereochemistry showcased in the alkylation with oxazolidinone **14**; however, this strategy would require the use of a α -halomethyl phenyl sulfone or sulfide as the electrophile. Neither one of these electrophiles have been extensively used in enolate alkylations. We are aware of only one example (with PhSCH₂I⁹) using an oxazolidinone-derived enolate by Baker and co-workers in their synthesis of milbemycin β_3 in which they required extended reaction times (5 d at -20°C) to provide only 30% of the target compound.^{10,11} We had hoped that the matched nature of compound **14** might prove advantageous to the reaction rate and chemical yield. We were pleased to observe that the reaction proceed smoothly and in high levels of diastereoselectivity (1 h, 70% yield, 10:1 dr). Lithium borohydride reduction of **18** followed by sulfide oxidation and deoxygenation provided the desired coupling partner **3**. We also investigated an alternate route that provided more direct access to **3**. HWE olefination of aldehyde **4** generated the unsaturated sulfone **21** in good yield. Subsequent conjugate addition using Me₂CuLi directly gave the sulfone **3**. While the diastereoselectivity in the cuprate addition step was disappointing (approx. 1:1 dr), the brevity of this cuprate route is highly attractive (just 2 steps from aldehyde **4**). It should also be noted that we are aware of only limited examples of conjugate addition to vinyl sulfones using cuprate or organolithium reagents.¹² Recently, Feringa and co-workers have reported an elegant catalytic, asymmetric protocol for addition to α,β -unsaturated pyridyl sulfones using a monodentate phosphoramidite ligand, copper triflate and dialkylzincs; however, they were unable to facilitate the addition of dimethylzinc due to its reduced reactivity.¹³

The completion of the synthesis of cermizine D (**1**) is shown in Scheme 5. Deprotonation of sulfone **3** using LDA followed by addition of aldehyde **4** gave the hydroxy-sulfone as a mixture of diastereomers at both C₇ and C₈. It was critical that the deprotonation step be conducted with short reaction times (e.g. 1 min) as unwanted intramolecular addition to the neighboring Boc-moiety was observed with extended reaction times. The unwanted C₇ diastereomer **22** could be recycled via oxidation followed by reduction with NaBH₄ to regenerate a near equal (1.5:1) ratio (**22**:**2**). It should be noted that we have not independently confirmed the relative stereochemistry at C₇ in either compound **22** or **2**. Next, direct desulfurization of the hydroxy sulfone **2** was cleanly accomplished using Raney Ni.¹⁴ This desulfurized product proved unstable in our hands – attempts to purify by silica gel chromatography or derivatize as its Mosher ester (to establish the absolute configuration at C₇) led to decomposition. Fortunately, deprotection of the crude product followed by cyclization¹⁵ generated cermizine D (**1**) in reasonable yield (60%, 3 steps). Comparison of

our synthetic **1**•TFA material with the ^1H / ^{13}C NMR and optical rotation data reported by Takayama and co-workers^{3,16} showed that our synthesized material was in good agreement.

In summary, a short, practical synthesis of cermizine D has been developed. Key steps in this synthesis include an organocatalyzed, heteroatom Michael addition to construct the common intermediate **4** and a sulfone-aldehyde coupling / desulfurization sequence to join the two subunits. The brevity of the outlined approach [9 steps with cuprate addition strategy (*via* **21**) or 16 steps using the PhSCH_2I alkylation approach (*via* **18**)] compares favorably to Takayama's 18-step approach. In addition, the common intermediate strategy provides access to over 85% of the carbon skeleton (14 of 16 carbon atoms) and both nitrogen atoms of cermizine D.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
ORTEP Representation of the X-Ray Crystallographic Data of Compound 15.

Scheme 2.
Synthesis of Common Intermediate.

Scheme 3.
Synthesis of Sulfone Fragment.

Scheme 4.
Improved Routes to Sulfone Fragment.

Scheme 5.
Completion of the Synthesis.