

Expedient Enantioselective Synthesis of
Cermizine D

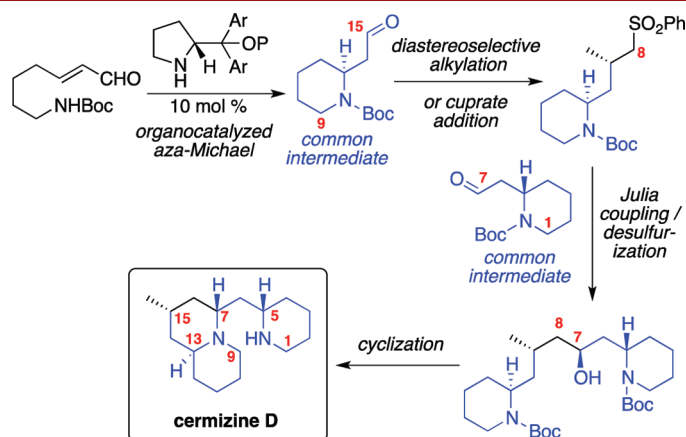
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ABSTRACT



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 ($7.5 \mu\text{g/mL}$).¹ Related cermizine alkaloids have attracted the attention of several laboratories.² To date, one elegant 18-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

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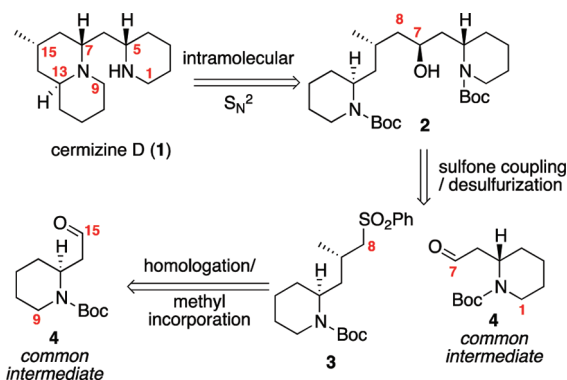
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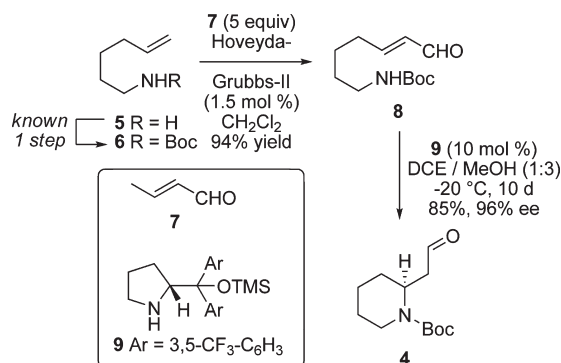
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Scheme 1. Retrosynthetic Analysis



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

Scheme 2. Synthesis of Common Intermediate



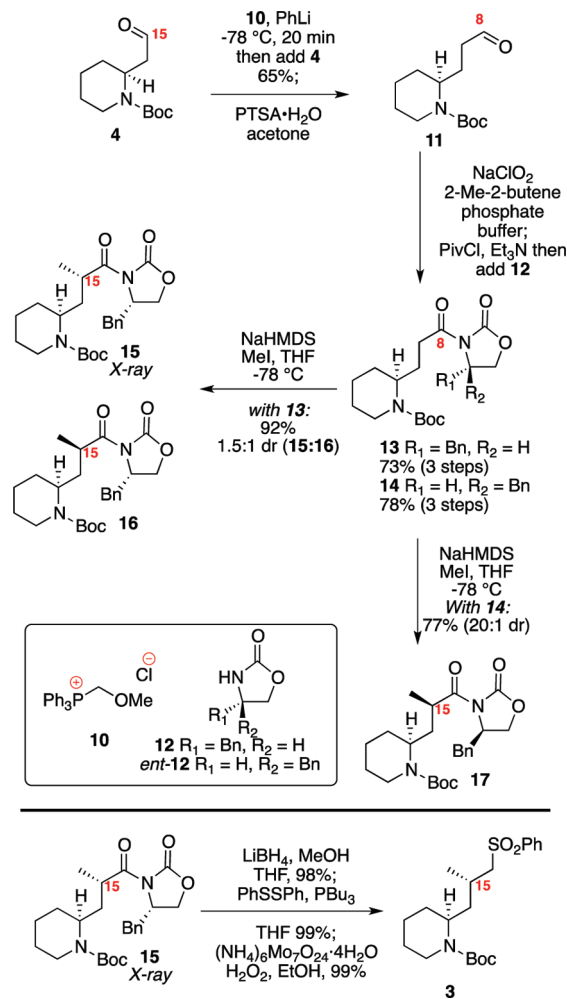
Our first generation approach for the conversion of the common intermediate **4** into sulfone **3** is shown in Scheme 3. Homologation via Wittig olefination and enol ether cleavage revealed aldehyde **11**. Pinnick oxidation followed by coupling with Evans oxazolidinone **12** generated compound **13**. 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 mismatched 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

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oxazolidinone **15** followed by conversion to the sulfide and oxidation generated the sulfone **3**.

Scheme 3. Synthesis of Sulfone Fragment



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 an 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 $PhSCH_2I$)⁹ 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 $-20^\circ C$) to provide only 30% of the target compound.^{10,11} We had hoped that the

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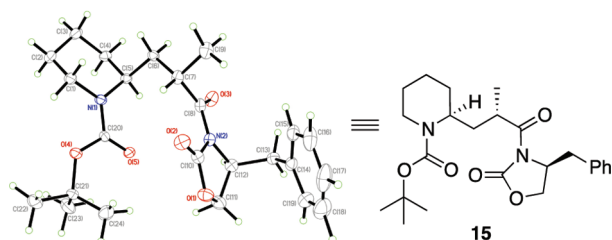
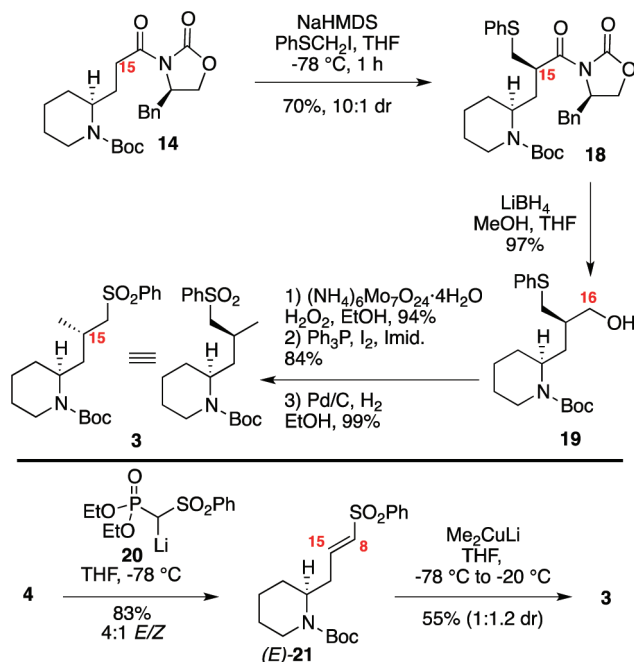


Figure 1. ORTEP representation of the X-ray crystallographic data of compound **15**.

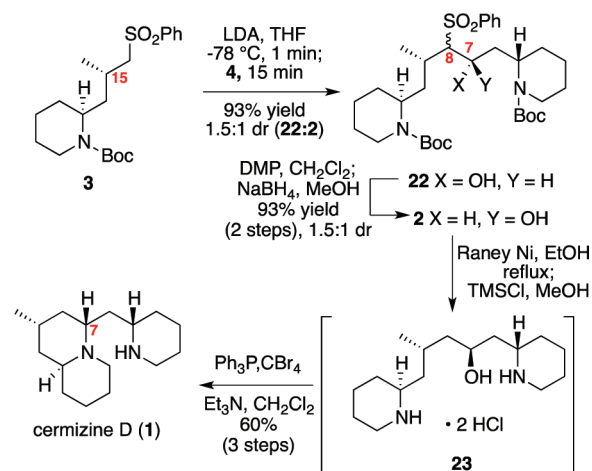
matched nature of compound **14** might prove advantageous to the reaction rate and chemical yield. We were pleased to observe that the reaction proceeded smoothly and in high levels of diastereoselectivity (1 h, 70% yield, 10:1 dr). Lithium borohydride reduction of **18** followed by sulfide oxidation and deoxygenation provided the desired coupling partner **3**. We also investigated an alternate route that provided more direct access to **3**. Horner–Wadsworth–Emmons olefination of aldehyde **4** generated the unsaturated sulfone **21** in good yield. Subsequent conjugate addition using Me_2CuLi directly gave the sulfone **3**. While the diastereoselectivity in the cuprate addition step was disappointing (approximately 1:1 dr), the brevity of this cuprate route is highly attractive (just two 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 C_7 and C_8 . 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 C_7 diastereomer **22** could be recycled via oxidation followed by reduction with NaBH_4 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 C_7 in either compound **22** or **2**. Next, direct desulfurization of the hydroxy sulfone **2** was cleanly accomplished using

Scheme 4. Improved Routes to Sulfone Fragment



Scheme 5. Completion of the Synthesis



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 C_7) led to decomposition. Fortunately, deprotection of the crude product followed by cyclization¹⁵ generated cermizine D (**1**) in reasonable yield (60%, three steps). Comparison of our synthetic **1**•TFA material with the $^1\text{H}/^{13}\text{C}$ NMR and optical rotation data

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(16) While not stated in the original isolation data, the spectroscopic data were also reported as the TFA salt of cermizine D (**1**). Hirasawa, Y. *Private communication*.

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 PhSCH₂I 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.

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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** are also provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.