ORGANIC LETTERS

2012
Vol. 14, No. 6
1596–1599

Expedient Enantioselective Synthesis of Cermizine D

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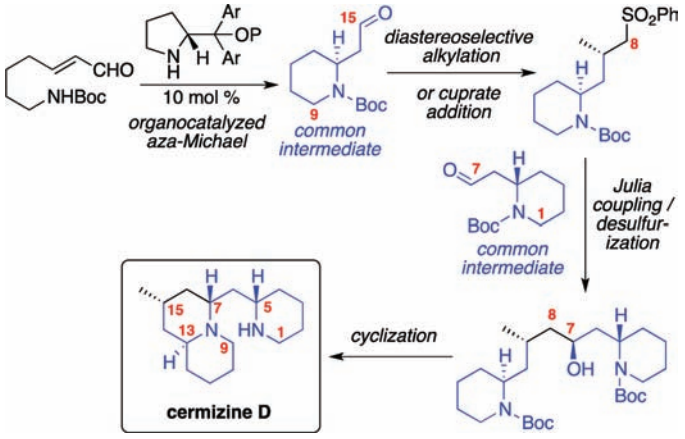
Received February 11, 2012

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 aginst murin lymphoma L1210 cells (7.5 μg/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 C_7−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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(2) (a) Snider, B. B.; Grabowski, J. F. *J. Org. Chem.* **2007**, *72*, 1039–1042. (b) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394–8395. (c) Beng, T. K.; Gawley, R. E. *J. Am. Chem. Soc.* **2010**, *132*, 12216–12217. (d) Cheng, G.; Wang, X.; Su, D.; Liu, H.; Liu, F.; Hu, Y. *J. Org. Chem.* **2010**, *75*, 1911–1916. (e) Taber, D. F.; Guo, P.; Pirnot, M. T. *J. Org. Chem.* **2010**, *75*, 5737–5739. (f) Chou, S.-S. P.; Chung, Y.-C.; Chen, P.-A.; Chiang, S.-L.; Wu, C.-J. *J. Org. Chem.* **2011**, *76*, 692–695.

(3) (a) Nishikawa, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 1987–1990. (b) Nishikawa, Y.; Kitajima, M.; Kogure, N.; Takayama, H. *Tetrahedron* **2009**, *65*, 1608–1617.

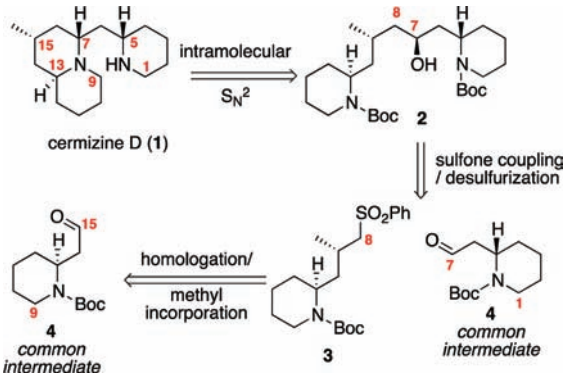
(4) Carlson, E. C.; Rathbone, L. K.; Yang, H.; Collett, N. D.; Carter, R. G. *J. Org. Chem.* **2008**, *73*, 5155–5158.

(5) (a) Fustero, S.; Jimnez, D.; Moscard, J.; Cataln, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283–5286. (b) Gerasyuto, A. I.; Hsung, R. P.; Sydorenko, N.; Slafer, B. *J. Org. Chem.* **2005**, *70*, 4248–4256.

(6) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797. (b) Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T. Y.; Liu, P.; Zhou, J. *Org. Lett.* **2009**, *11*, 1999–2002.

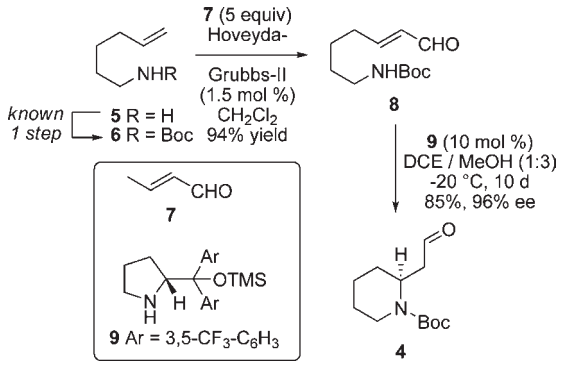
10.1021/ol300342n © 2012 American Chemical Society
Published on Web 02/28/2012

Scheme 1. Retrosynthetic Analysis



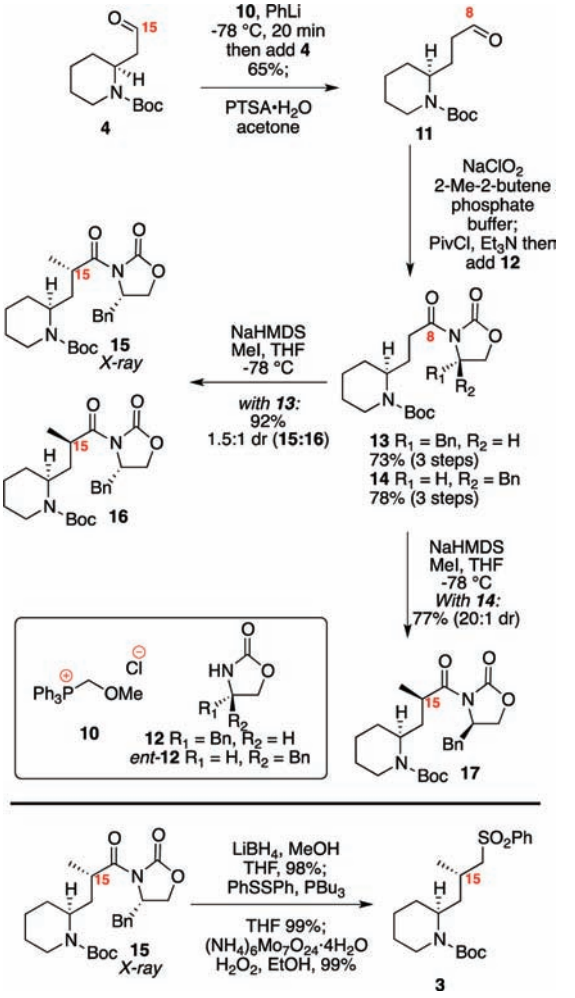
slight modification of our previously reported conditions[4]) employing catalyst **9**[6] cleanly generated the piperidine **4** in 85% yield and 96% ee as determined by chiral HPLC analysis.[5,7]

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. Homogolation via Wittig olefination and enol ether cleavage revealed aldehyde **11**. Pinnick oxidation followed by coupling with Evans oxazolidinone **12** generated compound **13**. Diastereoselective alkylation[8] 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 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 C_{15} 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 °C) to provide only 30% of the target compound.[10,11] We had hoped that the

(7) Fustero and co-workers have also developed a related, organocatalyzed approach to compound **4**. Fustero, S.; Moscardó, J.; Sánchez-Roselló, M.; Flores, S.; Guerola, M.; del Pozo, C. *Tetrahedron* **2011**, *67*, 7412–7417.

(8) Jin, Y.; Liu, Y.; Wang, Z.; Kwong, S.; Xu, Z.; Ye, T. *Org. Lett.* **2010**, *12*, 1100–1103.

(9) Trost, B. M.; King, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 408–422.

(10) (a) Baker, R.; O'Mahony, M. J.; Swain, C. *J. Chem. Soc., Chem. Commun.* **1985**, 1326–1328. (b) Baker, R.; O'Mahony, M. J.; Swain, C. J. *J. Chem. Soc., Perkin Trans 1* **1987**, 1623–1633.

(11) Three reports of thio-Michael addition/diastereoselective protonation to α,β-unsaturated acyl oxazolidinones have also been disclosed: (a) Tseng, T.-C.; Wu, M.-J. *Tetrahedron: Asymmetry* **1995**, *6*, 1633–1640. (b) Raghavan, S.; Tony, K. A. *J. Org. Chem.* **2003**, *68*, 5002–5005. (c) Rana, N. K.; Singh, V. K. *Org. Lett.* **2011**, *13*, 6520–6523.

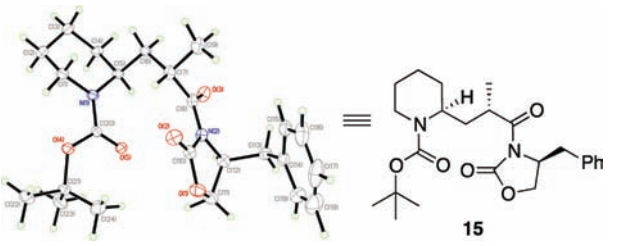
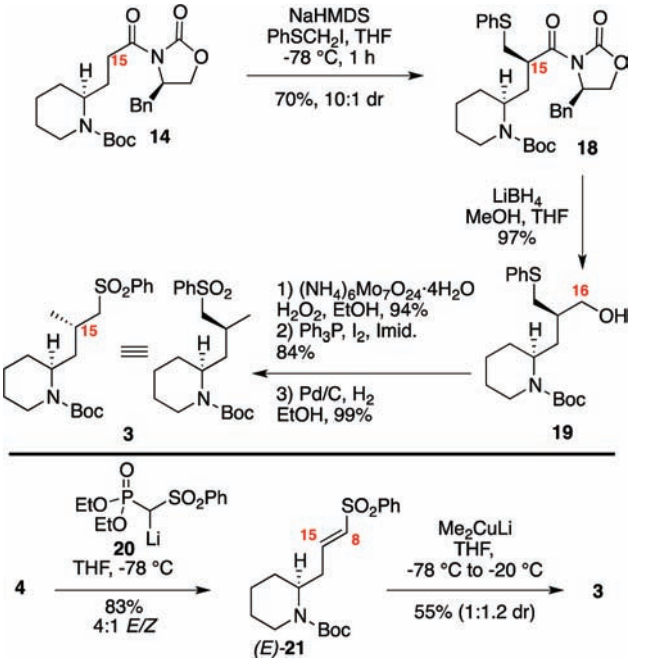


Figure 1. ORTEP representation of the X-ray crystallographic data of compound **15**.

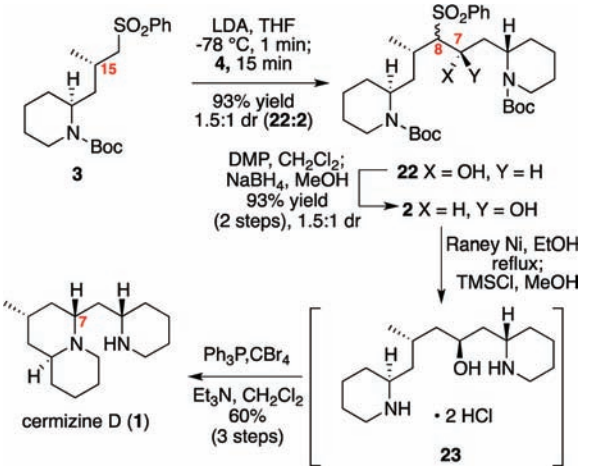
matched nature of compound **14** might prove advantageous to the reaction rate and chemical yield. We were pleased to observe that the reaction proceeded smoothly and in high levels of diastereoselectivity (1 h, 70% yield, 10:1 dr). Lithium borohydride reduction of **18** followed by sulfide oxidation 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 cyclization[15] generated cermizine D (**1**) in reasonable yield (60%, three steps). Comparison of our synthetic **1**•TFA material with the $^1H/^{13}C$ NMR and optical rotation data

(12) (a) De Chirico, G.; Fiandanese, V.; Marchese, G.; Naso, F.; Sciacovelli, O. *J. Chem. Soc., Chem. Commun.* **1981**, 523–524. (b) Ichikawa, Y.; Isobe, M.; Masaki, H.; Kawai, T.; Goto, T. *Tetrahedron* **1987**, *43*, 4759–4766. (c) Dominguez, E.; Carretero, J. C. *Tetrahedron Lett.* **1993**, *34*, 5803–5806.

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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 $PhSCH_2I$ 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.

Acknowledgment. Financial support was provided by the National Institutes of Health (NIH) (GM63723). The National Science Foundation (CHE-0722319) and the Murdock Charitable Trust (2005265) are acknowledged for their support of the NMR facility. We thank Dr. Lev N. Zakharov (OSU and University of Oregon) for X-ray crystallographic analysis of compound **15** as well as Professor Max Deinzer and Dr. Jeff Morré (OSU) for mass spectra data. Finally, the authors are grateful to Professor James D. White (OSU) and Dr. Roger Hanselmann (Rib-X Pharmaceuticals) for their helpful discussions.

Supporting Information Available. Complete experimental procedures are provided, including ^{1}H and ^{13}C 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.