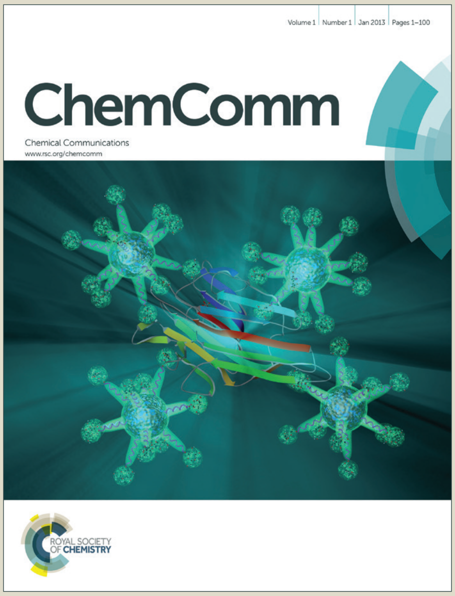
# ChemComm

Accepted Manuscript



Volume 1 | Number 1 | Jan 2013 | Pages 1–100

ChemComm

Chemical Communications

www.rsc.org/chemcomm

ROYAL SOCIETY OF CHEMISTRY

This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

*Accepted Manuscripts* are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name
RSCPublishing

ARTICLE

# Gram-scale route to phlegmarine alkaloids: rapid total synthesis of (-)-cermizine B†

Cite this: DOI: 10.1039/x0xx00000x

Ben Bradshaw*, Carlos Luque-Corredera and Josep Bonjoch*

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

The synthesis of the *Lycopodium* alkaloid (-)-cermizine B (**1**), which establishes its absolute configuration, is achieved by combining asymmetric organocatalysis and an uninterrupted eight-step reaction sequence, followed by a final reduction step. This "pot-economy" strategy provides access to the *cis*-phlegmarine stereoparent embedded in **1** for the first time, rapidly and on a gram-scale.

One of the main impediments to accessing viable quantities of complex natural products in a timely and cost-effective manner is the 'stop-and-go' approach,[1] which requires a purification step after each synthetic operation. This undoubtedly involves the greatest investment of time and materials in any total synthesis endeavour and is a major source of waste generation. An alternative strategy involving a series of tandem reactions[2] in combination with 'pot-economy'[3] offers a potent solution to this problem. By eliminating the need for work-up and product isolation between successive synthetic steps, it becomes possible to complete an entire multi-step sequence in a single pot,[4] a process that approaches Wender's definition of an 'ideal synthesis.[5]

With this aim in mind, and based on our recent work on asymmetric synthesis of decahydroquinolines using organocatalysis,[6] we decided to apply the aforementioned "one-pot" operational approach in the field of *Lycopodium* alkaloids[7] (Fig. 1). This group of structurally diverse compounds have elicited major interest in recent years for their potential use in the treatment of severe neurodegenerative diseases.[7d,8] A great number of approaches to the main classes of *Lycopodium* alkaloids,[9] namely lycopodine, lycodine, and fawcettimine, have been developed, but there are limited synthetic entries to their biogenetic precursors, the phlegmarine alkaloids. To date, the synthesis of *cis*-phlegmarine alkaloids has been limited to lycoposerramine Z,[6a,10] whereas synthetic efforts towards *trans*-phlegmarines include the pioneering studies of McLean,[11] the attainment of lycoposerramine X by Takayama[10,12] and the comprehensive phlegmarine synthesis reported by Comins.[13] Considering that all the previous syntheses, apart from our recent work,[6a] have required more than twenty steps, a more efficient entry to the phlegmarine alkaloids would not only be a desirable goal in itself, but could also be used as a platform to access members of the other classes of *Lycopodium* alkaloids.

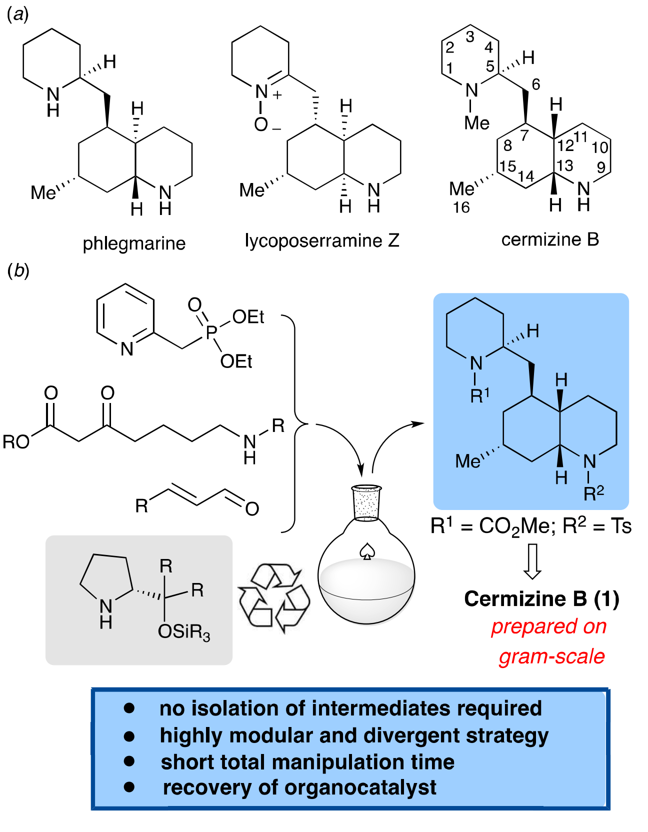


Fig. 1 (a) Structures of phlegmarine alkaloids (the three stereoparents), including the biogenetic numbering. (b) Strategy for synthesis of cermizine B

*Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain. E-mail: benbradshaw@ub.edu; josep.bonjoch@ub.edu*

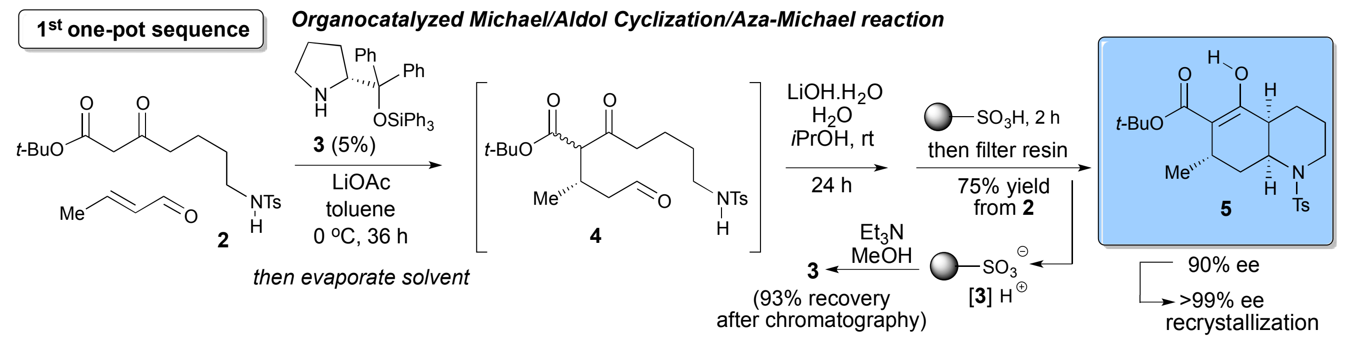
† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data and copies of NMR spectral data. See DOI: 10.1039/b000000x/

We herein report a highly efficient synthesis and the absolute configuration of the cis phlegmarane-type alkaloid cermizine B (1),[14] the first of a member of the *cis*-phlegmarine subset with an anti stereochemical relationship between the ring-fusion hydrogens and the prototypical methyl substituent (C-16) in the decahydroquinoline ring.

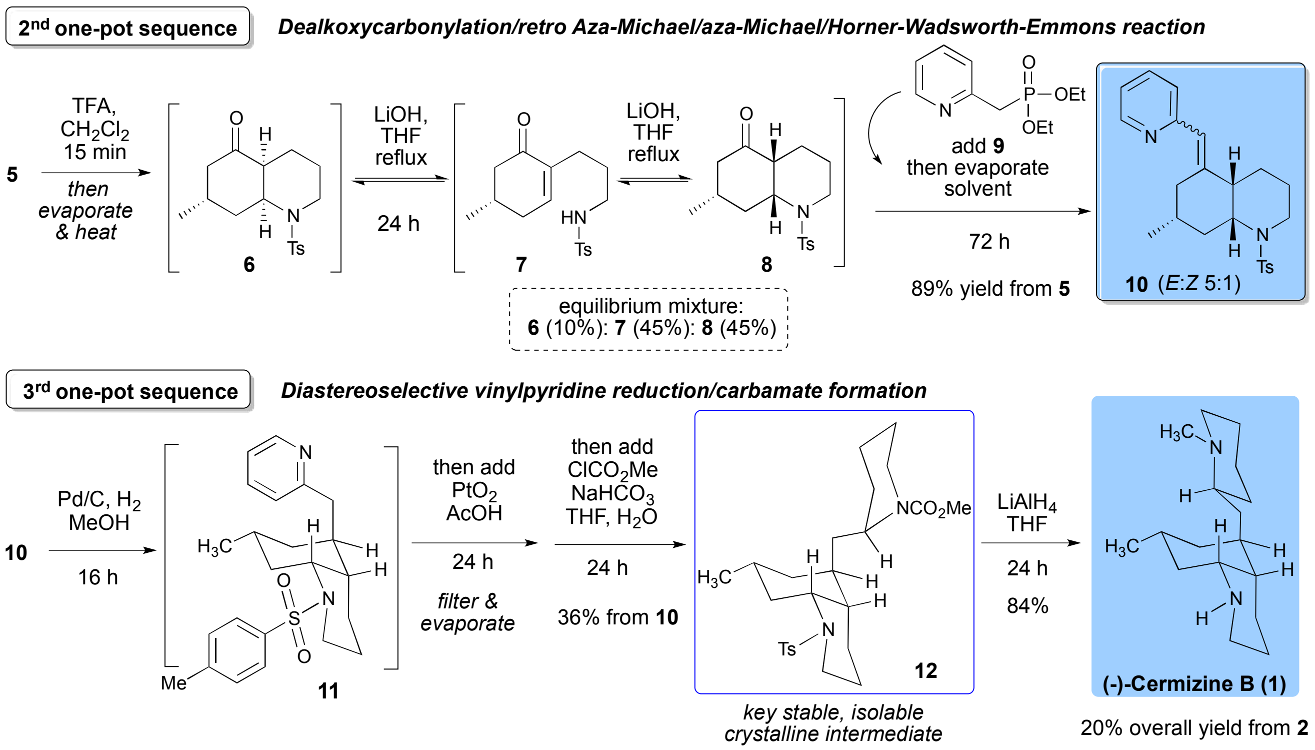
The overall process was initially developed by dividing the synthesis into three sets of tandem reactions (Scheme 1), which were subsequently fused into a single sequence. The first one-pot operation began with β-keto ester **2**, which underwent an organocatalyzed Michael reaction in the presence of just 5% loading of the modified Hayashi catalyst **3**,[15] improving our preliminary published results.[6a] Removal of the solvent and treatment of **4** with LiOH in the presence of *i*PrOH and water led to the tandem aldol condensation/intramolecular aza-Michael reaction, which delivered *cis*-decahydroquinoline **5**. With the aim of minimizing waste and preventing downstream accumulation in the eventual uninterrupted sequence, the reaction mixture was treated with a sulfonic acid resin, eliminating the need for any work-up procedure by removing the basic residues and also allowing the capture and recuperation of the organocatalyst in excellent yield. We believe that this solution is a simple alternative to recycling the catalyst via immobilization on solid support. It should be noted that not only did the modified catalyst (triphenylsilyl instead of trimethylsilyl diphenylprolinol ether) improve the enantiomeric excess but its significantly more robust nature also proved essential for its recovery with the acidic resin at the end of the reaction. Decahydroquinoline **5** was isolated in 75% overall yield[16] from keto ester **2** in 90% ee.

The second one-pot sequence (Scheme 2) commenced with treatment of **5** with TFA, followed by evaporation and heating to effect the complete decarboxylation of the resulting keto acid moiety. Direct addition of LiOH and THF to the reaction pot, followed by refluxing overnight resulted in the retro aza-Michael ring opening of **6** to **7**, and subsequent partial closure to the more stable decahydroquinoline **8**,[6b] with the required stereochemistry present in cermizine B. Although the closure did not got to completion, giving an equilibrium mixture of **6**:**7**:**8** (1:4.5:4.5, respectively), it was found that direct addition of phosphonate **9** led to a chemoselective reaction with **8**, and by means of a shift in the equilibrium, vinylpyridine **10** was formed exclusively as an inconsequential mixture of *Z*/*E* isomers (1:5 ratio). Hydrogenation (see below) of each isomer gave the same result, obviating the need to separate them. Furthermore, we noted that this coupling reaction performed better if carried out under solvent-free conditions, giving **10** in an excellent 89% yield over the entire sequence from **5**. For the final one-pot sequence, alkene **10** was hydrogenated in the presence of Pd/C in MeOH, which delivered the hydrogen selectively from the bottom face of the molecule in a 5:1 ratio to give **11**. We believe that the facial selectivity was primarily influenced by the tosyl group, which effectively blocked the top face of **10**. Removal of the tosyl group prior to the hydrogenation led to the selective reduction from the top face of the molecule to give the opposite stereochemistry. Notably, this provides the stereochemical arrangement of another phlegmarine alkaloid (huperzine M).[17] Hydrogenation of the pyridine ring was then accomplished by direct addition of $PtO_2$ and AcOH to the reaction mixture containing **11**.[18] Filtration, evaporation and carbamation with methyl chloroformate gave **12** as a stable, readily purified epimeric mixture. Finally, treatment with $LiAlH_4$ converted the carbamate into the required methyl group and smoothly removed the tosyl group to give cermizine B (**1**), which showed NMR spectroscopic data identical to those reported for the natural product (see ESI). The overall yield of the complete sequence was 20%. The data obtained for **1** $[\alpha]_D$ = -3.1 (*c* 0.7, MeOH) also confirmed that the absolute configuration depicted in Figure 1 corresponds to that of the natural product (-)-cermizine B {lit[14] $[\alpha]_D$ -2.0 (*c* 0.6, MeOH)}.[19]

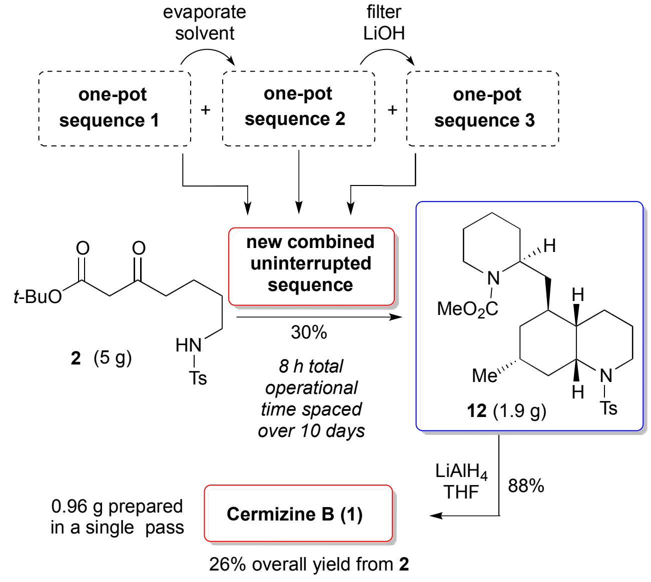
After the successful completion of the synthesis via a sequence involving 3 one-pot reactions, we sought to eliminate the remaining purification steps until carbamate **12**, which would render the whole process even more efficient (Scheme 3). Thus, after treatment with the resin at the end of the first one-pot sequence, the solvent was removed by evaporation and the resulting material was fed directly into the second set of tandem reactions, and then, after subsequent removal of the LiOH by filtration, into the third set. Reduction of this enantioenriched material, i.e. **12** (after a single purification step to remove *epi*-**12**), with $LiAlH_4$ then took place in 88% yield to give 0.96 g of the target cermizine B (**1**) from just 5 g of the starting β-keto ester **2**. By eliminating the aforementioned



Scheme 1 Optimized synthesis of *cis*-decahydroquinoline **5**.


2nd one-pot sequence
Dealkoxycarbonylation/retro Aza-Michael/aza-Michael/Horner-Wadsworth-Emmons reaction
5
TFA, CH2Cl2 15 min
then evaporate & heat
6
LiOH, THF reflux
24 h
7
LiOH, THF reflux
8
equilibrium mixture: 6 (10%): 7 (45%): 8 (45%)
add 9 then evaporate solvent
72 h
89% yield from 5
10 (E:Z 5:1)
3rd one-pot sequence
Diastereoselective vinylpyridine reduction/carbamate formation
10
Pd/C, H2 MeOH
16 h
11
then add PtO2 AcOH
24 h
filter & evaporate
then add ClCO2Me NaHCO3 THF, H2O
24 h
36% from 10
12
key stable, isolable crystalline intermediate
LiAlH4 THF
24 h
84%
(-)-Cermizine B (1)
20% overall yield from 2

Scheme 2 Total synthesis of (-)-cermizine B (**1**).


evaporate solvent
filter LiOH
one-pot sequence 1
one-pot sequence 2
one-pot sequence 3
new combined uninterrupted sequence
2 (5 g)
30%
8 h total operational time spaced over 10 days
12 (1.9 g)
LiAlH4 THF
88%
0.96 g prepared in a single pass
Cermizine B (1)
26% overall yield from 2

| nmo | $Y_{PBF}$ [%] | $Y_{PMO}$ [%] | $P_f$ |
|---|---|---|---|
| 9 | 76 | 86 | 6 |

Scheme 3 Pot-economy synthesis of cermizine B on a gram-scale and summary of the process according to Jørgensen's notation (ref 4c).

purification procedures, the overall yield for the new integrated sequence was increased to 26%, and could be completed in only 8 h of operational time, spaced over 10 days. To evaluate the overall efficiency of the process we applied the notation introduced by Jorgensen for one-pot reactions[4c] (see Scheme 3). The most striking feature of the uninterrupted sequence from the starting material to the precursor of cermizine B is that it consists of eight consecutive reactions for eight manual operations (nmo) and only one final purification. For the total synthesis of cermizine B, which required an additional step and purification, the values of $Y_{PBF}$ (76% yield per bond formed) and $Y_{PMO}$ (86% yield per manual operation) indicate that each step in this synthesis proceeded in high yield. The very high value of the purification factor ($P_f$ = 6), which denotes the number of purifications avoided, is also noteworthy. The considerable difference in the number of required steps compared with previous approaches to phlegmarane-type alkaloids underlines the efficiency and simplicity offered by asymmetric organocatalytic one-pot cascades.

In summary, a highly efficient, enantioselective total synthesis of cermizine B (**1**) was completed using a carefully orchestrated series of tandem reactions and the principles of pot economy. Our route to cermizine B constitutes the first synthesis of this type of *cis*-phlegmarine alkaloids. The convergent decahydroquinoline synthetic entry was key to the successful development of this concise, sustainable eight-step procedure that has allowed a gram scale synthesis of the natural product.[20] Considering the flexible, highly convergent and modular nature of this methodology, it could also be used to access the other phlegmarine alkaloids by changing stereomotifs in the decahydroquinoline core. Furthermore, it should enable the rapid synthesis of other *Lycopodium* alkaloids and analogs for the development of comprehensive structure-activity relationships of this important class of compounds.

Financial support for this research was provided by Project CTQ2010-14846/BQU from the Ministry of Economy and Competitiveness of Spain.

## Notes and references

1 (*a*) A. M. Walji and D. W. C. MacMillan, *Synlett*, 2007, 1477; (b) N. J. Green and M. S. Sherburn, *Aust. J. Chem.,* 2013, **66**, 267.

2 (*a*) C. Grondal, M. Jeanty and D. Enders, *Nature Chem*., 2010, **2**, 167; (*b*) L. M. Ambrosini and T. H. Lambert, *ChemCatChem*, 2010, **2**, 1373; (*c*) C. M. R. Volla, I. Atodiresei and M. Rueping, *Chem. Rev.,* 2014, **114**, 2390.

3 (*a*) H. Ishikawa, T. Suzuki and Y. Hayashi, *Angew. Chem. Int. Ed.*, 2009, **48**, 1304; (*b*) H. Ishikawa, T. Suzuki, H. Orita, T. Uchimaru and Y. Hayashi, *Chem. Eur. J.*, 2010, **16**, 12616; (*c*) P. A. Clarke, S. Santos and W. H. C. Martin, *Green Chem.*, 2007, **9**, 438; (*d*) Y. Hayashi and S. Umemiya, *Angew. Chem. Int. Ed.*, 2013, **52**, 3450

4 (*a*) H. Ishikawa, M. Honna and Y. Yahashi, *Angew. Chem. Int. Ed.*, 2011, **50**, 2824; (*b*) C. Vaxelaire, P. Winter and M. Christmann, *Angew. Chem. Int. Ed.*, 2011, **50**, 3605; (*c*) L. Albrecht, H. Jiang and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2011, **50**, 8492; (*d*) T. Mukaiyama, H. Ishikawa, H. Koshino and Y. Hayashi, *Chem. Eur. J.*, 2013, **19**, 17789.

5 (*a*) P. A. Wender and B. L. Miller, *Nature*, 2009, **460**, 197; (*b*) P. A. Wender, *Tetrahedron*, 2013, **69**, 7529. (c) P. A. Wender, *Nat. Prod. Rep.,* 2014, **31**, 433.

6 (*a*) B. Bradshaw, C. Luque-Corredera and J. Bonjoch *Org. Lett.*, 2013, **15**, 326; (*b*) B. Bradshaw, C. Luque-Corredera, G. Saborit, C. Cati viela, R. Dorel, C. Bo and J. Bonjoch, *Chem. Eur. J.*, 2013, **19**, 13881.

7 (*a*) X. Ma and D. R. Gang, *Nat. Prod. Rep.* 2004, **21**, 752; (*b*) Y. Hirasawa, J. Kobayashi and H. Morita, *Heterocycles* 2009, **77**, 679; (*c*) P. Siengalewicz, J. Mulzer and U. Rinner, *The Alkaloids* 2013, **72**, 1; (*d*) R. A. Murphy and R. Sarpong, *Chem. Eur. J.* **2014**, **20**, 42.

8 J. Xu, M. H. Lacoske and E. A. Theodorakis, *Angew. Chem. Int. Ed.* 2014, **53**, 956.

9 (*a*) C. H. Heathcock, E. Kleinman and E. S. Binkley, *J. Am. Chem. Soc.*, 1982, **104**, 1054; (*b*) D. F. Fischer and R. Sarpong, *J. Am. Chem. Soc.*, 2010, **132**, 5926; (*c*) B. B. Liau and D. M. Shair, *J. Am. Chem. Soc.*, 2010, **132**, 9594; (*d*) J. Ramharter, H. Weinstabl and J. Mulzer, *J. Am. Chem. Soc*., 2010, **132**, 1433.

10 T. Tanaka, N. Kogure, M. Kitajima and H. Takayama, *J. Org. Chem.*, 2009, **74**, 8675.

11 A. Leniewski, J. Szychowski and D. B. MacLean, *Can. J. Chem.* 1981, **59**, 2479.

12 For the synthesis of lycoposerramines V and W, embodying a tetrahydroquinoline framework, see: T. Shigeyama, K. Katakawa, N. Kogure, M. Kitajima and H. Takayama, *Org. Lett.*, 2007, **9**, 4069.

13 (*a*) D. L. Comins, A. H. Libby, R. Al-awar and C. Foti, *J. Org. Chem.*, 1999, **64**, 2184; (b) B. H. Wolfe, A. H. Libby, R. Al-awar, C. J. Foti and D. L. Comins, *J. Org. Chem.*, 2010, **75**, 8564.

14 For isolation of cermizines A-D, see: H. Morita, Y. Hirasawa, T. Shinzato, and J. Kobayashi, *Tetrahedron* 2004, **60**, 7015.

15 (a) Y. Wang, P. Li, X. Liang, and J. Ye, *Adv. Synth. Catal.*, 2008, **350**, 1383; (b) E. Gómez-Bengoa, A. Landa, A. Lizarraga, A. Mielgo, M. Oiarbide and C. Palomo, *Chem. Sci.*, 2011, **2**, 353.

16 Notably, along with decahydroquinoline **5**, small amounts of non-cyclized product (i. e. **7**) and material with the β-keto ester in the keto rather than enol form were also isolated. While the presence of these products reduced the yield of **5**, not separating them in the uninterrupted sequence allowed their conversion to the final product, thereby effectively increasing the yield of the first sequence.

17 W.-Y. Gao, Y.-M.Li, S.-H. Jiamg and D.-Y. Zhu, *Helv. Chim. Acta*, 2008, **91**, 1031.

18 It should be noted there is no effective asymmetric version for reducing alkylpyridines. A preliminary examination of the methodology of Glorius using a pyridine analogous to **9** with a chiral auxiliary at C-6 was not sufficiently satisfactory. For the procedure, see: F. Glorius, N. Spielkamp, S. Holle, R. Goddard and C. W. Lehman, *Angew. Chem. Int. Ed.*, 2004, **43**, 2850.

19 To further confirm the stereochemistry at the stereogenic center at C-5, we also prepared the non-natural *epi*-cermizine B from *epi*-**12** to compare their NMR data (see ESI, Tables S1 and S2) and optical rotation $[\alpha]_D = +50.0$ (*c* 0.95, MeOH).

20 C. A. Kuttruff, M. D. Eastgate and P. S. Baran, *Nat. Prod. Rep*., 2014, **31**, 419.