Volume 50 | Number 54 | 11 July 2014 | Pages 7077–7206

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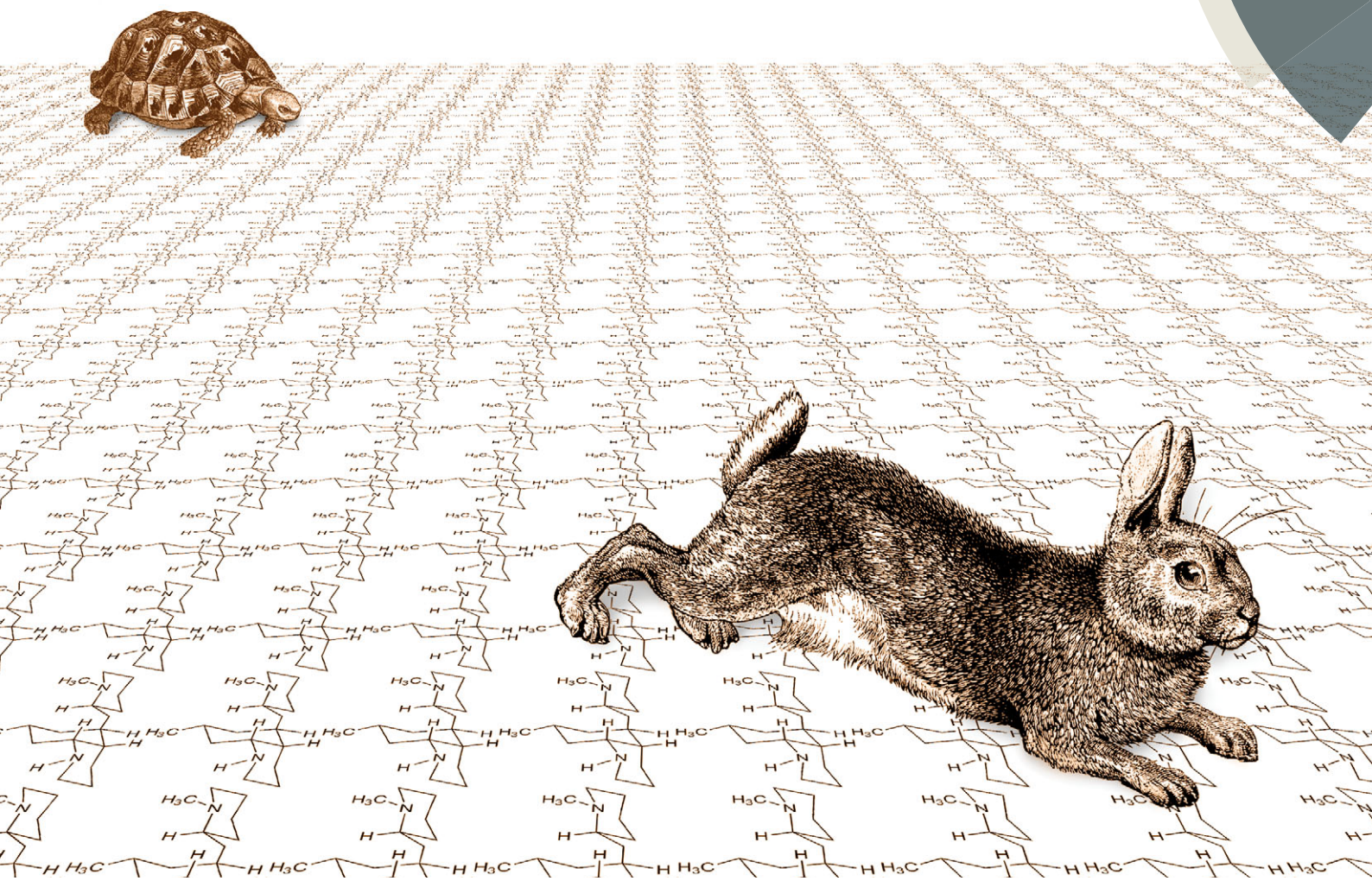

ISSN 1359-7345

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A gram-scale route to phlegmarine alkaloids: rapid total synthesis of (−)-cermizine B†

Cite this: *Chem. Commun.*, 2014, **50**, 7099

Received 6th March 2014,
Accepted 3rd April 2014

DOI: 10.1039/c4cc01708k

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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 MacLean,[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.

We herein report a highly efficient synthesis and the absolute configuration of the *cis* phlegmarane-type alkaloid cermizine B (**1**),[14]

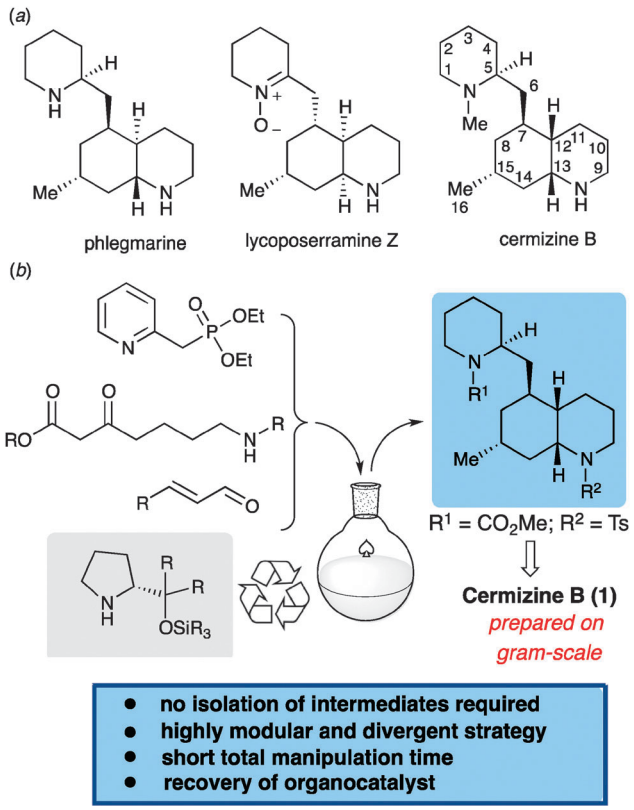

Fig. 1 (a) Structures of phlegmarine alkaloids (the three stereoparents), including the biogenetic numbering. (b) Strategy for synthesis of cermizine B.

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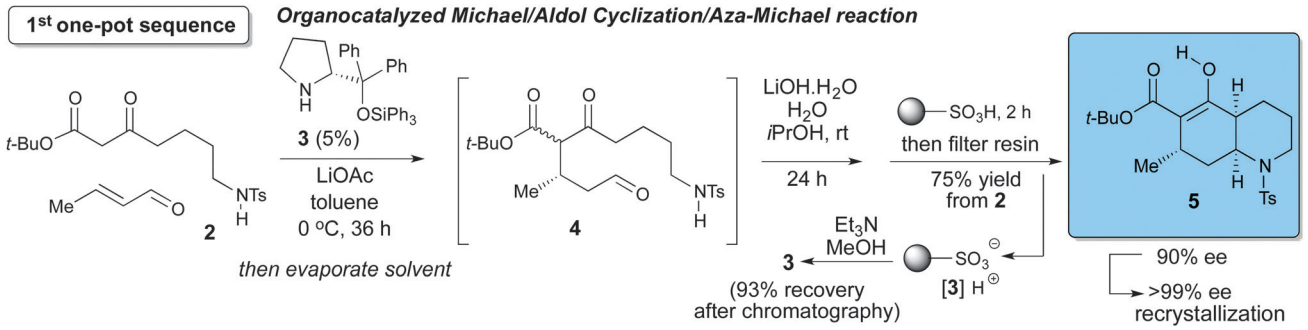
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and copies of NMR spectral data. See DOI: 10.1039/c4cc01708k



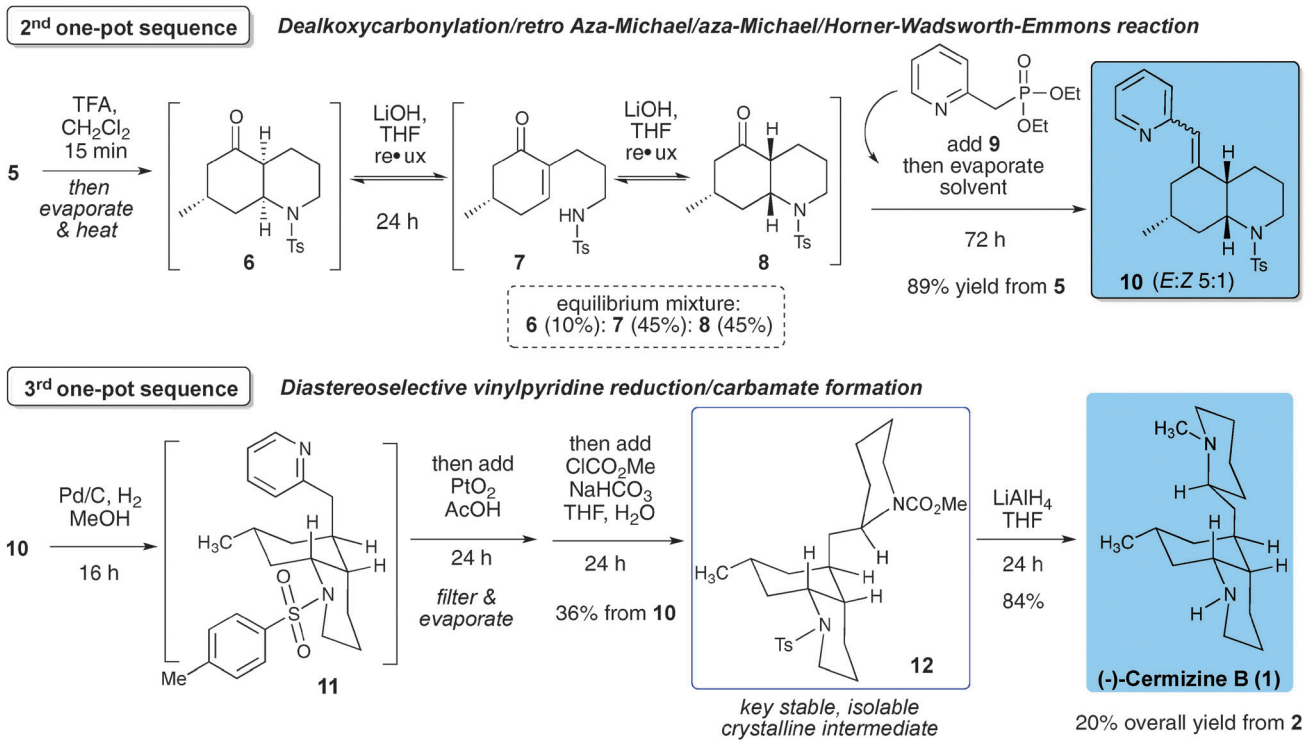
Scheme 1 Optimized synthesis of *cis*-decahydroquinoline **5**.

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.

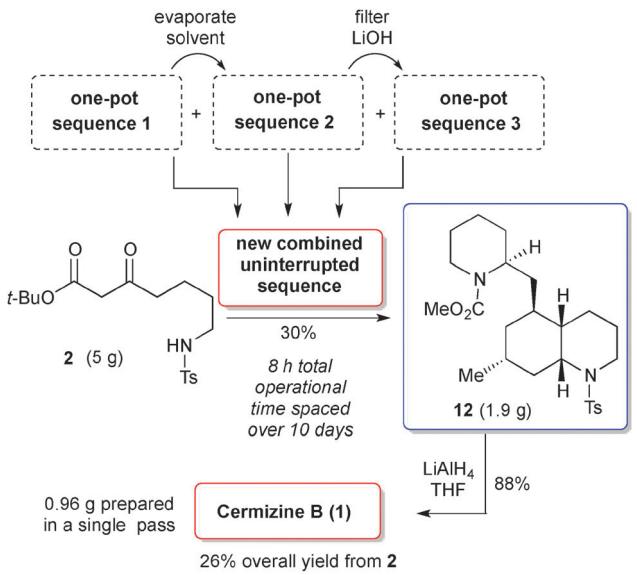
The overall process was initially developed by dividing the synthesis into three sets of tandem reactions (Scheme 1), which were subsequently fused into a single sequence. The first one-pot operation began with β-keto ester **2**, which underwent an organocatalyzed Michael reaction in the presence of 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 iPrOH 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 a 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** with 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 go 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 yield of 89% 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 Fig. 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 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 Jørgensen 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



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



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).

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 a comprehensive structure–activity relationship of this important class of compounds.

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

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