

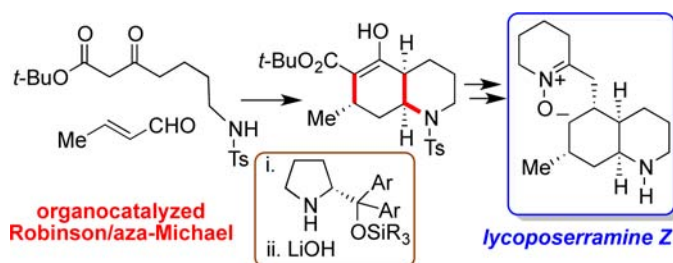
cis-Decahydroquinolines via Asymmetric Organocatalysis: Application to the Total Synthesis of Lycoposerramine Z

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ABSTRACT



A concise synthesis of the *Lycopodium* alkaloid lycoposerramine Z is reported. Key to the strategy is a one-pot organocatalyzed Michael reaction followed by a domino Robinson annulation/intramolecular aza-Michael reaction promoted by LiOH, leading to enantiopure *cis*-decahydroquinolines.

Lycoposerramine Z (**1**), isolated by Takayama in 2006,¹ belongs to a small class of phlegmarine-type *Lycopodium* alkaloids (Figure 1) that serve as biogenetic intermediates between pelletierine and all other alkaloids of this complex family with around 250 congeners.² Interestingly, **1** incorporates an unusual nitron moiety,³ which has been postulated to act as a radical trap, halting destructive cascades initiated by free radicals, and hence has potential application in neurodegenerative diseases.⁴ In 2009, starting from the chiral pool, Takayama's group completed the first total synthesis of **1**,⁵ which remains to date the only synthesis of

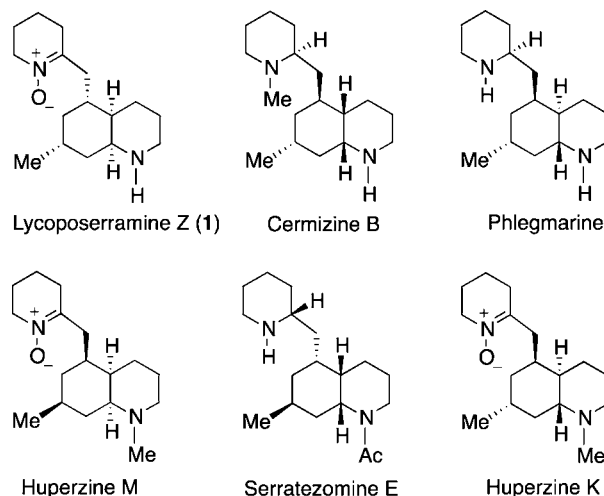


Figure 1. Phlegmarine-type *Lycopodium* alkaloids.

a phlegmarine alkaloid with a *cis*-ring fused decahydroquinoline unit.⁶

We herein report a concise, enantioselective synthesis of lycoposerramine Z (**1**). The cornerstone of our synthetic

(1) Katakawa, K.; Kitajima, M.; Yamaguchi, K.; Takayama, H. *Heterocycles* **2006**, 69, 223–229.

(2) (a) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, 21, 752–772. (b) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, 77, 679–729.

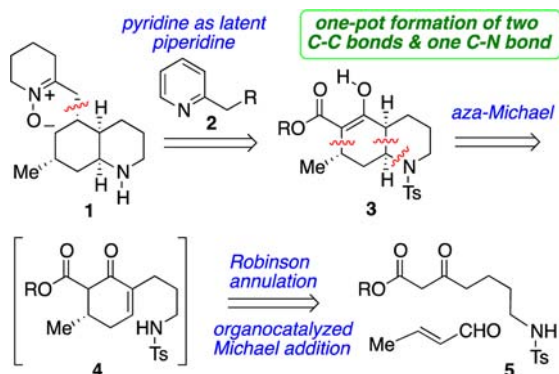
(3) The nitron group was later found in related compounds: Gao, W.; Li, Y.; Jiang, S.; Zhu, D. *Helv. Chim. Acta* **2008**, 91, 1031–1035.

(4) Sun, Y.; Yu, P.; Zhang, G.; Wang, L.; Zhong, H.; Zhai, Z.; Wang, L.; Wang, Y. *J. Neurosci. Res.* **2012**, 90, 1667–1669.

(5) Tanaka, T.; Kogure, N.; Kitajima, M.; Takayama, H. *J. Org. Chem.* **2009**, 74, 8675–8680.

(6) For the synthesis of related phlegmarines embodying the most usual trans-ring fusion in the decahydroquinoline ring, see: (a) Leniewski, A.; Szychowski, J.; MacLean, D. B. *Can. J. Chem.* **1981**, 59, 2479–2490. (b) Comins, D. L.; Libby, A. H.; Al-awar, R.; Foti, C. J. *J. Org. Chem.* **1999**, 64, 2184–2185. (c) Wolfe, B. H.; Libby, A. H.; Al-awar, R.; Foti, C. J.; Comins, D. L. *J. Org. Chem.* **2010**, 75, 8564–8570. (d) Reference 5.

Scheme 1. Retrosynthesis of Lycoposerramine Z



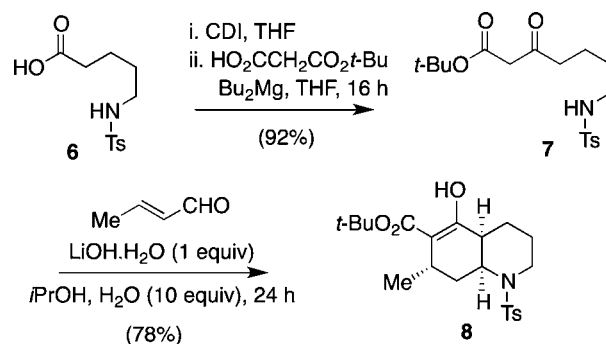
approach is a rapid asymmetric assembly of the azabicyclic core by a novel organocatalyzed diastereo- and enantioselective one-pot tandem synthesis of decahydroquinolines. In this process two C–C bonds and one C–N bond (Scheme 1) and three stereogenic centers are created in a single step.^{7,8}

As outlined in Scheme 1, we envisaged that the piperidine appendage could be introduced by the coupling of a methylpyridine **2** with a 5-oxodecahydroquinoline. The β -keto ester **3** precursor of the latter would be formed via a Robinson annulation of the simple acyclic keto ester **5** through an initial organocatalyzed Michael addition, followed by an in situ intramolecular aza-Michael reaction of the generated cyclohexenone **4**. We speculated that the retention of the ester group in **3** would be essential for the success of our strategy, helping to stabilize the β -amino ketone moiety and prevent side reactions.^{9,10}

The synthesis of **1** began with the *N*-tosylation of the commercially available 5-aminopentanoic acid, and the resulting acid **6** was subjected to a homologation with mono-*tert*-butylmalonate under Masamune-type conditions¹¹ to give **7** (77% over two steps, Scheme 2). The reaction conditions for the key Robinson annulation/intramolecular aza-Michael biscyclization process to achieve decahydroquinoline **8** from **7** and crotonaldehyde

were first examined in a nonasymmetric version. After considerable experimentation¹² we found that the decahydroquinoline ring could be generated in a straightforward one-pot reaction using LiOH·H₂O (1 equiv) in *i*PrOH¹³ in the presence of water (10 equiv).¹⁴ We were delighted to find that under these conditions decahydroquinoline *rac*-**8** was delivered in only one step and as a single diastereoisomer. As predicted, the retention of the ester group stabilized the compound by forming the enolic tautomer, which effectively acts as a locking group, preventing the ring opening by a retro aza-Michael reaction in the basic reaction medium or in the purification step (silica gel chromatography).

Scheme 2. Synthesis of *rac*-**8**



To carry out the reaction in asymmetric form, the Hayashi catalyst¹⁵ was chosen to promote the initial organocatalyzed Michael addition, after which the tandem cyclization conditions (LiOH) were applied.^{16,17} A screening of solvents indicated that toluene was the optimal choice. Several other catalysts,¹⁸ mainly diaryl-prolinol silyl ethers,¹⁹ were then screened, and the slight superiority of triphenylsilyl derivative **9**²⁰ led to its selection (Table 1, entry 1).

The reaction was further refined by lowering the temperature (entries 2 and 3) and the use of additives was

(7) For organocatalytic cascade reactions in total synthesis, see: (a) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167–178. (b) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183–188. (c) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278–1293.

(8) For recent enantioselective synthesis of *cis*-decahydroquinolines, see: (a) Ito, T.; Overman, L. E.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 3272–3273. (b) Kagugawa, K.; Nemoto, T.; Kohno, Y.; Yamada, Y. *Synthesis* **2011**, 2540–2548. (c) Amat, M.; Navio, L.; Llor, N.; Molins, E.; Bosch, J. *Org. Lett.* **2012**, *14*, 210–213. (d) Gärtner, M.; Qu, J.; Helmchen, G. *J. Org. Chem.* **2012**, *77*, 1186–1190.

(9) We have observed that direct azacyclization upon an enone to give 5-oxodecahydroquinolines is troublesome since the cyclized compound is in equilibrium with the ring-opened α,β -unsaturated ketone: Borregan, M. Ph.D. Thesis, University of Barcelona, Spain, 2009.

(10) No intramolecular aza-Michael process leading to 5-oxodecahydroquinolines has been described so far. For interesting results related to this field, see: (a) Brosius, A. D.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 440–441. (b) Taber, D. F.; Joshi, P. V.; Kanai, K. *J. Org. Chem.* **2004**, *69*, 2268–2271.

(11) (a) Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72–73. (b) Hodgson, D. M.; Labande, A. L.; Pierard, Y. T. M.; Castro, M. A. E. *J. Org. Chem.* **2003**, *68*, 6153–6159.

(12) For instance, *t*-BuOK in *t*-BuOH was not sufficiently effective, despite its frequent use in Robinson reactions: Chong, B.; Ji, Y.; Oh, S.; Yang, J.; Baik, W.; Koo, S. *J. Org. Chem.* **1997**, *62*, 9323–9325.

(13) These reaction conditions were adapted from those used by Baran (LiOH (0.1 equiv), *i*PrOH, rt, 24 h) in the synthesis of cryptone: Chen, K.; Ishihara, Y.; Galán, M. M.; Baran, P. S. *Tetrahedron* **2010**, *66*, 4738–4744. It should be noted that these previously published conditions were unsuccessful when applied to **3** and crotonaldehyde.

(14) Water was necessary to drive the aza-Michael reaction to completion. In its absence significant amounts of the ring-opened Robinson annulation product were obtained (20–30%).

(15) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215.

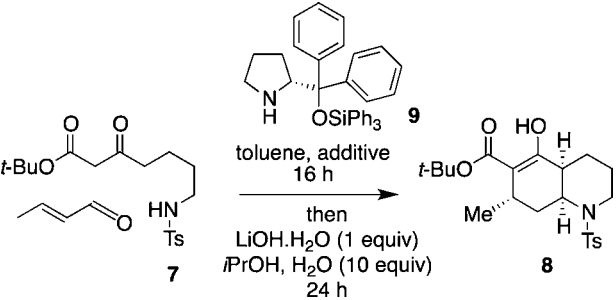
(16) The classical procedure to achieve cyclohexenones developed by Jørgensen using an initial organocatalyzed Michael addition followed by treatment with TsOH was unsuccessful when starting from **3**: Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. *Chem. Commun.* **2006**, 4928–4930.

(17) For an organocatalytic initial Michael reaction and Robinson annulation that retains the ester group, see: Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475–5479.

(18) The results of the initial screening of solvents and catalysts are summarized in the Supporting Information.

(19) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248–264.

Table 1. Screening Conditions for the Organocatalyzed Robinson Annulation/aza-Michael Reaction^a



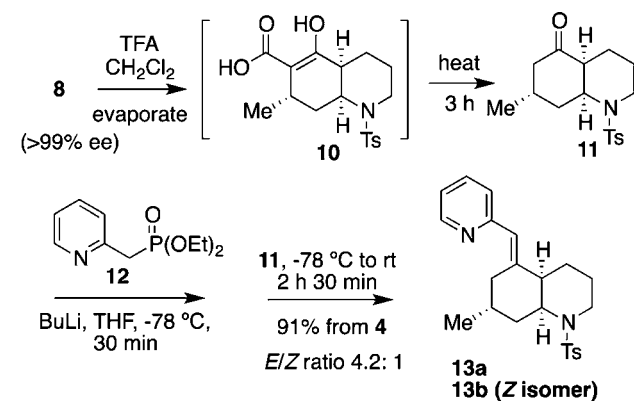
entry	additive (equiv)	temp (°C)	yield (%)	ee (%)
1	none	rt	57	80
2	none	0	57	82
3	none	-20	49	82
4	H ₂ O (10)	0	69	84
5	LiOAc (0.5)	0	72	85
6	KOAc (0.5)	0	58	83
7	BzOH (0.5)	0	43	80
8	H ₂ O (10)/LiOAc (0.5)	0	63	80
9	LiOAc (1)	0	66	82

^a 20% catalyst loading of **5** was used in a 0.1 M solution of **3**. Toluene was evaporated before proceeding with the tandem biscyclization.

investigated (entries 4–10). The addition of LiOAc²¹ (entry 5) was essential for obtaining a good conversion yield (72% for three bond-forming reactions) and enantiomeric ratio (>92:8). It is worth mentioning that the combination of LiOAc and another good additive, water (entry 4), were not synergistic, giving results (entry 8) inferior to those with their individual use.

In general, in comparison with bulkier groups, the small size of the methyl group sets a limit to the maximum enantioselectivity (in our case 84–85% ee) in organocatalyzed Michael additions.¹⁶ However, we were able to access (+)-**8** in enantiopure form by recrystallization of **8** from MeOH,²² which provided the product in >99% ee (first crop, 65% recovery).

Scheme 3. Coupling of the Methylpyridine Fragment



With enantiopure decahydroquinoline (+)-**8** in hand, we set about converting it into the natural product lycoposerramine **Z**. Removal of the *tert*-butyl ester locking group with TFA gave ketoacid **10**, which upon azeotropic removal of TFA with toluene by heating underwent decarboxylation to ketone **11** (Scheme 3). The material was used immediately in the next step without any purification²³ and added directly to a solution of the lithium anion of phosphonate **12**²⁴ to give vinylpyridine derivatives **13** in excellent yield (91%). A mixture of *Z/E* isomers (~1:4.2) was observed,^{25,26} which were separated by chromatography. However, this turned out to be inconsequential since hydrogenation of the mixture or each isolated isomer gave the same all-*cis*-product **14** in which the hydrogen was delivered from the top face (see Scheme 4, which depicts the major isomer **13a**). Analysis of the ¹H and ¹³C NMR spectra of both *Z/E* diastereomers of the starting material (**13a** and **13b**) allowed us to establish that the preferred conformation of these compounds accommodates axial positioning of the methyl group, which avoids the allylic 1,3-strain²⁷ both for the exocyclic double bond (with the C(4)–C(4a) bond) and the *N*-tosyl group (with the C(8)–C(8a) bond).²⁸ This preferred conformation is involved in steric interactions that influence the diastereoselectivity of the hydrogenation process. The reduction led exclusively to decahydroquinoline **14**, in which the substituents at C(5) and C(7) are axially located according to NMR data. Thus, the crucial role of the axial methyl group in the process was clearly established, as it sterically impedes hydrogenation from the bottom face.

With all four introduced stereogenic centers now in place, the tosyl group was replaced by a Teoc group prior to the installation of the sensitive nitron moiety.^{29,30} Thus, the tosyl group was removed (HBr, phenol) to give **15**, which was converted into the Teoc carbamate **16** (Scheme 5). Reduction of the pyridine ring with PtO₂/AcOH gave the piperidine **17** as an inconsequential mixture of epimers

(20) For the first reported use of this catalyst, see: Wang, Y.; Li, P.; Liang, X.; Ye, J. *Adv. Synth. Catal.* **2008**, *350*, 1383–1389. For its preparation and subsequent application, see: Gomez-Bengoa, E.; Landa, A.; Lizarraga, A.; Mielgo, A.; Oiarbide, M.; Palomo, C. *Chem. Sci.* **2011**, *2*, 353–357.

(21) For an interesting study on the effect of LiOAc in organocatalyzed Michael reactions, see: Duce, S.; Mateo, A.; Alonso, I.; García Ruano, J. L.; Cid, M. B. *Chem. Commun.* **2012**, *48*, 5184–5186.

(22) The use of EtOH gave a certain amount of transesterification products. For related phenomena, see: Witzeman, J. S.; Nottingham, W. D. *J. Org. Chem.* **1991**, *56*, 1713–1718.

(23) Fortunately, under the reaction conditions the product did not undergo a retro aza-Michael reaction. However, it should be noted that upon prolonged manipulation (e.g., silica gel chromatography, etc.) the ring-opened product began to be observed.

(24) Gan, X.; Binyamin, I.; Rapko, B. M.; Fox, J.; Duesler, E. N.; Paine, R. T. *Inorg. Chem.* **2004**, *43*, 2443–2448.

(25) Using the lithium anion of 2-(trimethylsilyl)methylpyridine (ref 6a) in a Peterson reaction, compounds **13** were isolated in the same ratio but with a slightly lower yield (80%).

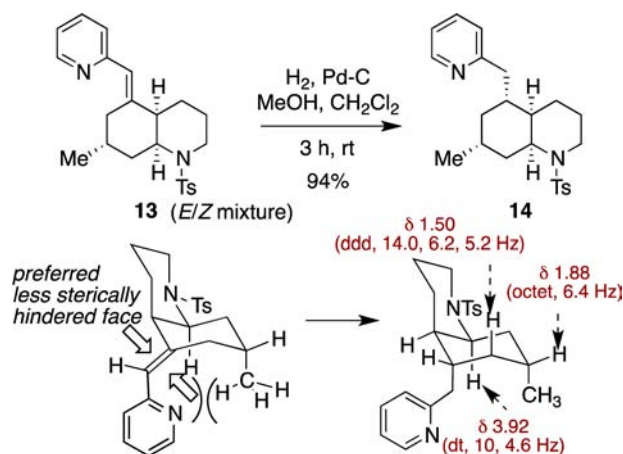
(26) Interestingly, this diastereoselectivity is the reverse of that observed in the related 2,5-dioxodecahydroquinoline system: see ref 6a.

(27) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1873.

(28) Booth, H.; Bostock, A. H. *J. Chem. Soc., Perkin Trans 2* **1972**, 615–621.

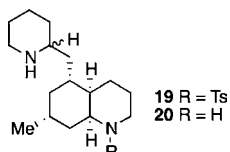
(29) This protecting group was used by Takayama in his synthesis of **1**, where it was shown that it could be removed in the presence of the sensitive nitron moiety.

Scheme 4. Diastereoselective Reduction of Alkene **13**



(not shown). This was oxidized with Na_2WO_4 /urea peroxide³¹ to give nitron **18**, which was identical to the final intermediate in Takayama's synthesis.⁵ Although the deprotection of **18** to lycoposerramine **Z** has already been reported, for the sake of a complete enantioselective total synthesis of **1**, the Teoc group was removed using TFA.^{32,33} The resulting (+)-lycoposerramine **Z** showed identical NMR spectroscopic data to those reported for the natural product,¹ as well as the same specific rotation value as synthetic **1**.⁵

(30) Attempts to avoid the exchange of the protecting groups via a biomimetic chemoselective oxidation of diamine **20** were unsuccessful. Diamine **20** was prepared via a one-pot hydrogenation of the vinylpyridine moiety of **13** to give piperidine **19**, from which the tosyl group was removed by treatment with LiAlH_4 (88% over two steps). Unfortunately, we were unable to chemoselectively oxidize the latter with Na_2MoO_4 ³¹ (0.5–1 equiv) to directly deliver lycoposerramine **Z** (**1**).

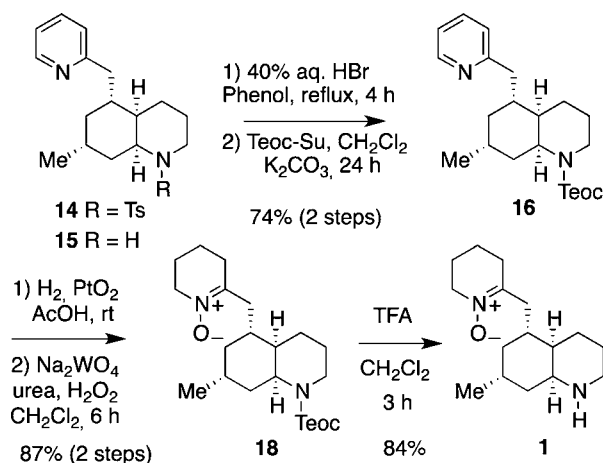


(31) Marcantoni, E.; Petrini, M.; Polimanti, O. *Tetrahedron Lett.* **1995**, 36, 3561–3562. See also: Ohtake, H.; Imada, Y.; Murahashi, S. *Bull. Chem. Soc. Jpn.* **1999**, 72, 2737–2754.

(32) (a) For deprotection of *N*-Teoc carbamates with TFA, see: Carpino, L. A.; Tsao, J.-H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc. Chem. Comm.* **1978**, 358–350. (b) For the stability of a nitron moiety to TFA, see: Medina, S. I.; Wu, J.; Bode, J. W. *Org. Biomol. Chem.* **2010**, 8, 3405–3417.

(33) This protocol greatly simplified the isolation procedure, avoiding the use of TASf or TBAF for the *N*-Teoc cleavage in **18**.

Scheme 5. Completion of the synthesis of lycoposerramine **Z**



In summary, we have described a short synthesis of lycoposerramine **Z**, which was completed in only 10 steps (20% overall yield)³⁴ from commercially available 5-aminopentanoic acid. Key to the success of the synthesis was a one-pot tandem organocatalyzed formation of decahydroquinolines, which allowed a rapid enantio- and diastereoselective assembly of the alkaloid core structure. We believe that the methodology presented here not only has the potential to provide access to numerous other *Lycopodium* alkaloids but also should prove applicable in the asymmetric synthesis of other important nitrogen-containing heterocyclic structures. Research in this direction is now underway.

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Supporting Information Available. Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra of the new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(34) This compares favorably with the 24 steps reported in the first synthesis of lycoposerramine **Z** (ref 5).

The authors declare no competing financial interest.