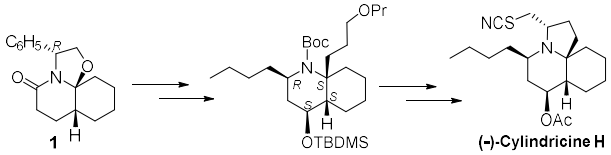
Total Synthesis of (–)-Cylindricine H

Miriam Piccichè, Alexandre Pinto, Rosa Griera, Joan Bosch, and Mercedes Amat*

Laboratory of Organic Chemistry, Faculty of Pharmacy and Food Sciences, and Institute of Biomedicine (IBUB), University of Barcelona, 08028-Barcelona, Spain

Supporting Information Placeholder



ABSTRACT: Starting from (*R*)-phenylglycinol-derived tricyclic lactam **1**, the enantioselective synthesis of (–)-cylindricine H is reported. From the stereochemical standpoint, the key steps are the stereoselective generation of the quaternary C_{10} stereocenter, the stereoselective introduction of the C_4 acetoxy and C_2 butyl substituents taking advantage of the lactam carbonyl functionality, and the assembly of the pyrrolidine ring with the required functionalized one-carbon chain at C_{13} by intramolecular opening of an epoxide.

Cylindricines are a small group of eleven marine alkaloids isolated in the early 1990s by Blackman et al. from the ascidian *Clavelina Cylindrica* off the coast of Tasmania.[1] They exhibit a pyrrolo[1,2-*j*]quinoline (cylindricines A, C–I, K) or pyrido[2,1-*j*]quinoline (cylindricines B, J) azatricyclic framework (Figure 1). Cylindricines A and C–G have in common a six-carbon lateral chain (except cylindricine G) and a ketone on the B ring but differ in the functionality of the one-carbon appendage on the pyrrolidine ring. Cylindricine A, with a chloromethyl group, is in equilibrium with its pyridoquinoline congener cylindricine B, presumably via an aziridinium intermediate. Cylindricines H–J, isolated from the same sources, have a butyl instead of a hexyl substituent at C-2 and were the first 4-acetoxycylindricines to be described. Cylindricines I and J bear an isothiocyanate at the one-carbon chain on the pyrrolidine ring, while cylindricines F–H have a thiocyanate, and are the only compounds isolated from ascidians with these functionalities. Finally, cylindricine K resembles cylindricine A but the carbocyclic A ring bears an unsaturated ketone. The optical rotation of these natural products was not determined and, consequently, their absolute configuration remained unassigned.

Since their isolation, owing to their unique structure, cylindricines have attracted significant attention among the synthetic community and currently the total synthesis of racemic cylindricines A–E has been achieved by several authors.[2] However, all the enantioselective syntheses reported to date focus on cylindricine C, which can be readily converted into cylindricines D and E.[3] No total synthesis of cylindricines F–K has been described in the literature.

In recent work we have explored the stereoselective generation of chiral aminoalcohol-derived oxazoloquinolone tricyclic lactams and their transformation into diversely substituted *cis*-decahydroquinolines (DHQs). The relevance of these enantiomeric scaffolds in the total synthesis of alkaloids having in common a DHQ nucleus was illustrated with the total

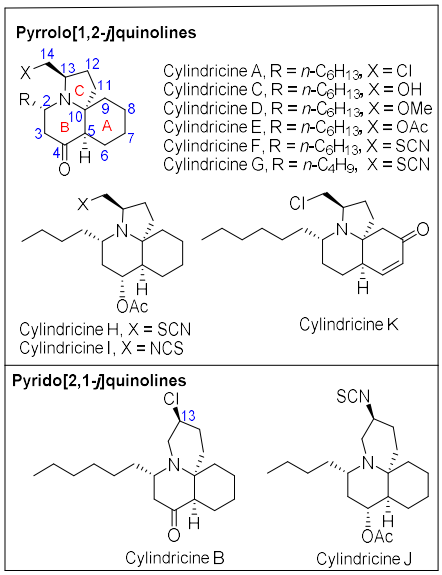
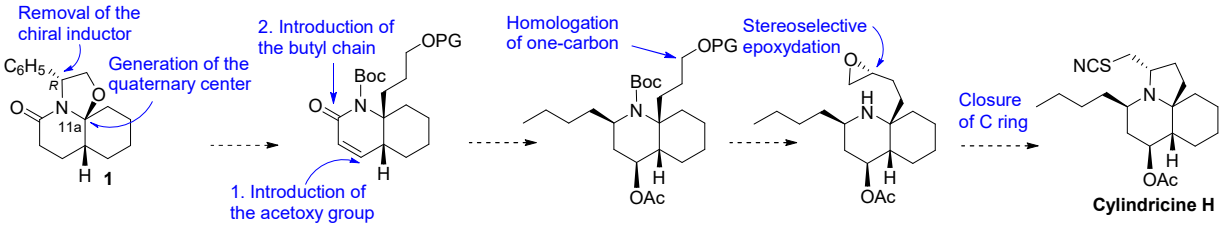


Figure 1. Alkaloids of the cylindricine group.

synthesis of *Myrioneuron*,[4] *Lycopodium*,[5] amphibian,[6] and marine alkaloids.[7] To further demonstrate the synthetic utility of these chiral tricyclic lactams, we decided to undertake the more challenging total synthesis of cylindricine H, which requires the formation of a quaternary carbon center embedded within a complex azatricyclic system.

With this purpose in mind, (*R*)-phenylglycinol-derived tricyclic lactam **1**,[8] bearing the DHQ moiety (rings AB of cylindricine H), was envisaged as the starting enantiomeric scaffold (Scheme 1). The synthetic strategy involves the initial generation of the quaternary stereocenter by the introduction of a functionalized carbon chain at the angular C_{11a} position (C_{10} of cylindricine) taking advantage of the *N*-acyl hemiaminal

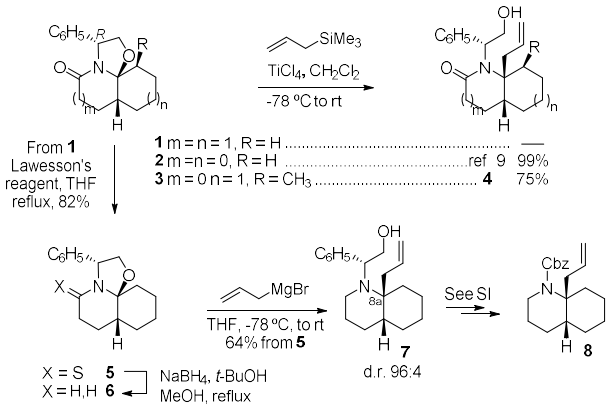
Scheme 1. **Synthetic Strategy**



function. The subsequent elaboration of this chain would allow the closure of the C ring in the final steps by intramolecular opening of an epoxide. The remaining acetoxy and butyl substituents would be stereoselectively incorporated by synthetic manipulation of the amide. A β-boration of the corresponding α,β-unsaturated amide, followed by oxidation of the C–B bond and acetylation of the resulting alcohol, would be used to stereoselectively introduce the acetoxy group, whereas activation of the amide, followed by the introduction of the butyl substituent and stereoselective reduction of the resulting enamide via an acyliminium salt, would install the lateral chain of cylindricine H.

Initial attempts to introduce an allyl chain at the angular position of tricyclic lactam **1** under the conditions reported by Danishefsky[9] from the 5-5-5 lactam **2** resulted in failure. The lower angular strain of the 5-6-6 system present in **1** due to the larger size of the B ring could account for this result. In fact, in our hands, under these conditions, the 5-5-6 tricyclic lactam **3** stereoselectively provided the allylated product **4**[10] in 75% yield (Scheme 2). To increase the reactivity of the hemiaminal moiety, the carbonyl of lactam **1** was selectively reduced by conversion into the corresponding thiolactam **5** followed by treatment with $NaBH_4$. Then, the quaternary stereocenter was satisfactorily installed by reaction of **6** with allylmagnesium bromide to give the desired allylated compound **7** in excellent stereoselectivity (d.r. 96:4) and good overall yield from **5**. The stereochemical outcome of the reaction was confirmed by conversion of **7** into the corresponding *N*-Cbz *cis*-DHQ **8** (see SI for details), which has been reported in the racemic series.[11]

Scheme 2. Allylation of Tricyclic Lactams by Amidoalkylation

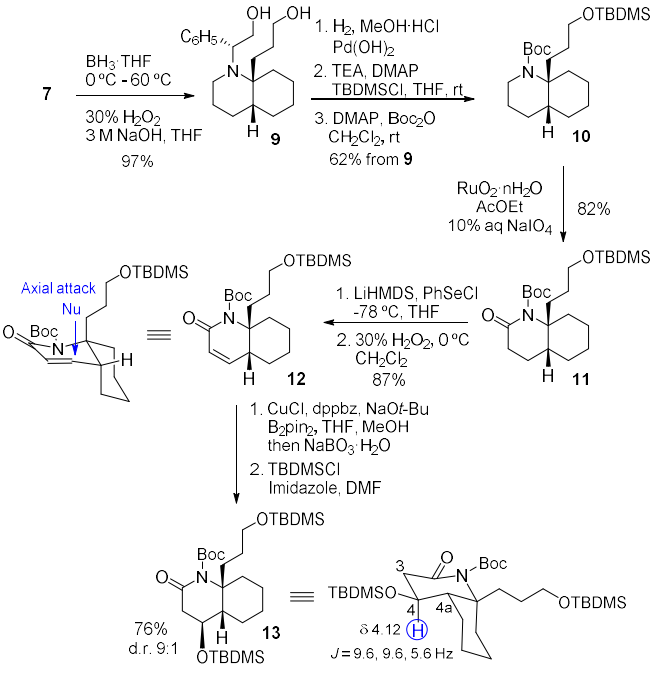


Our next goal was the removal of the chiral inductor from **7** and the refunctionalization of the C_2-position by oxidation to the corresponding lactam. Hydroboration-oxidation of the double bond present in **7** afforded diol **9** in excellent yield. The subsequent catalytic hydrogenation of **9** caused *N*-debenzylation, and the resulting amino-alcohol was sequentially protected as *O*-silyl and *N*-Boc derivatives, leading to the C_{8a} substituted *cis*-DHQ **10** in good overall yield. At this point, the lactam carbonyl was efficiently reinstalled by ruthenium-promoted oxidation to give *cis*-DHQ-2-one **11**.

We planned to incorporate the C_4 oxy substituent of cylindricine H by conjugate addition of a diboron reagent followed by oxidation of the C–B bond. The required unsaturated lactam **12** was prepared by phenylselenation of the lithium enolate of **11** and subsequent oxidation. Copper-catalyzed conjugate addition of bis(pinacolato)diboron to **12**, under the conditions reported by Yun,[12] and consecutive oxidation with sodium perborate furnished an alcohol, which was protected as silyl derivative without further purification. Compound **13**, with the appropriate configuration for the synthesis of cylindricine H, was obtained in excellent stereoselectivity and good overall yield (Scheme 3).

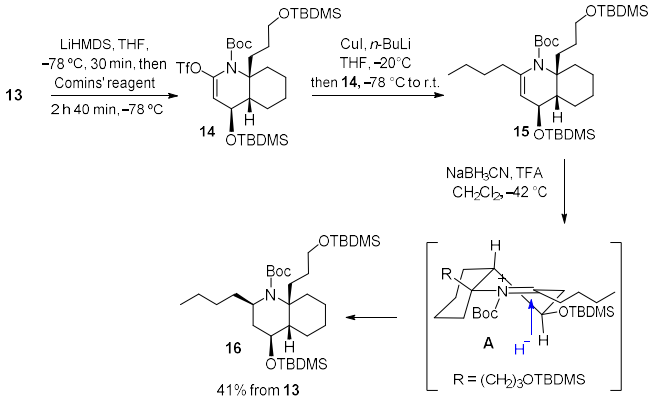
The stereochemical outcome of the β-boration reaction can be rationalized by considering an axial attack of the nucleophile, under stereoelectronic control,[13] on the more accessible convex face of the unsaturated lactam **12**, which adopts a conformation in which the C_{8a} chain is pseudoaxial with respect to the unsaturated ring to avoid the 1,3-diaxial destabilizing interactions that would appear in the alternative conformation.

Scheme 3. Stereocontrolled Introduction of the C_4 Substituent



For the introduction of the butyl chain, we used a procedure similar to the one we employed in our synthesis of gephyrotoxine 287C,[5b] consisting in the generation of an enecarbamate by coupling of a vinyl triflate with an organometallic reagent, followed by protonation and stereoselective reduction of the resulting acyliminium salt. It was assumed that the intermediate acyliminium salt **A** would adopt a conformation in which the OTBDMS and $(CH_2)_3$OTBDMS substituents would be equatorial with respect to the heterocyclic ring. An axial attack of the hydride ion, under stereoelectronic control, would lead to the required 2-butyl-DHQ, with the C_2 configuration of cylindricine H. Triflate **14** was prepared by treatment of lactam **13** with LiHMDS at –78 ºC for short reaction times and subsequent reaction of the lithium enolate with Comins' reagent at this temperature. The crude mixture was immediately treated with a solution of CuI and *n*-BuLi at low temperature, and the resulting enecarbamate **15** was reduced with $NaBH_3CN$–TFA without purification to give trisubstituted DHQ **16** in 41% overall yield for the three steps (Scheme 4).

Scheme 4. Stereoselective Introduction of the C_2 Butyl Chain

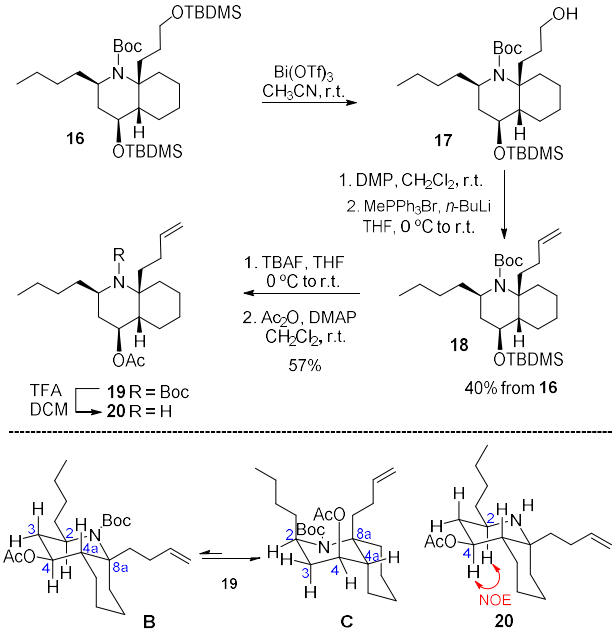


Unfortunately, the stereochemical outcome of the reaction could not be confirmed at this stage due to the overlapping of the signals corresponding to H-2 and H-4 in the ^{1}H NMR spectrum of **16**.

As mentioned before, it was envisaged that closure of the pyrrolidine C ring would be achieved by the regioselective intramolecular ring opening of an epoxide, a transformation that would also install a functionalized one-carbon appendage at C_{13}. This required a previous one-carbon homologation of the silyloxypropyl chain of **16**, which was accomplished by selective deprotection of the primary alcohol with bismuth(III) triflate followed by oxidation of **17** with the Dess–Martin periodinane and subsequent Wittig methylenation. Then, deprotection of the secondary alcohol present in **18** followed by acetylation afforded intermediate **19**, with the C_4 acetoxy substituent characteristic of cylindricine H (Scheme 5).

The ^{1}H NMR spectrum of **19** showed clear signals for H-2 and H-4 (δ 4.02 and 5.22, respectively), so at this point we decided to analyze the configurational identity of the C_2 stereocenter. We initially assumed that the DHQ system would adopt conformation **B**, in which the three substituents on the piperidine ring would be equatorial. However, NOESY experiments did not show a clear NOE effect of H-2 with either H-4 or H-4a. Moreover, the multiplicity of H-4 (triplet, with two

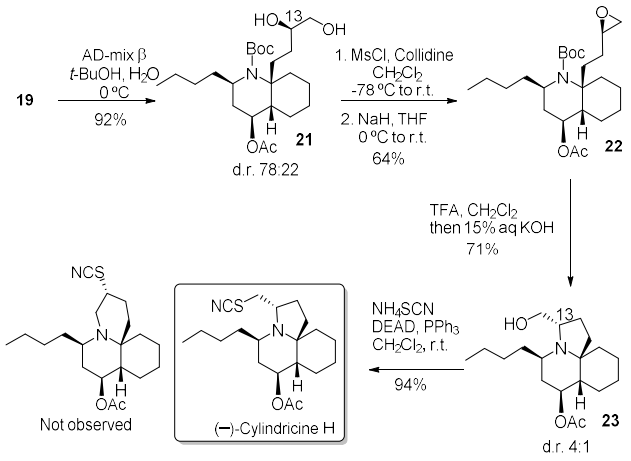
Scheme 5. Manipulation of the C_4 and C_{8a} DHQ Substituents and Determination of the Configuration at C_2



J of 7.5 Hz) did not agree with such a conformation **B**. These spectroscopic data led us to consider that the DHQ system would preferably adopt conformation **C** to avoid the $A^{1,3}$ interactions of the *N*-Boc group with the equatorial chains at the C_2 and C_{8a} positions in conformation **B**. To corroborate this hypothesis, the Boc protecting group of **19** was removed, giving rise to the secondary amine **20**, whose ^{1}H NMR spectrum was in agreement with the proposed structure. A NOESY experiment showed a clear NOE effect between H-2 and H-4, thus confirming that the configuration of the C_2 stereocenter was the one present in cylindricine H.

A Sharpless asymmetric dihydroxylation[14] of alkene **19**, followed by ring closure, was expected to stereoselectively generate epoxide **22**, which possesses the required configuration for the synthesis of cylindricine H. Indeed, treatment of a *t*-BuOH-H_2O solution of **19** with AD-mix-β at 0 ºC afforded in excellent yield a diastereomeric mixture (78:22 ratio) of diol **21** and its C_{13} epimer (cylindricine numbering), which could not be separated either by crystallization or chromatographic methods. Mesylation of the primary alcohol followed by basic treatment gave epoxide **22** as a mixture of epimers. Subsequent removal of the Boc protecting group with TFA and quenching of the reaction mixture with aqueous KOH regioselectively provided the desired tricyclic compound **23** as a 4:1 mixture of epimers at C_{13}, which could be satisfactorily separated by column chromatography. Finally, alcohol **23** was converted in excellent yield to cylindricine H by treatment with NH_4SCN under Mitsunobu conditions,[3f] thus accomplishing the first total synthesis of this natural product (Scheme 6). The thiocyanate analog of cylindricine J (a 6,6,6-system), arising from ring expansion of the pyrrolidine ring, was not observed. The spectroscopic data of our synthetic cylindricine H matched those previously reported for the natural product and its optical rotation was $[\alpha]^{20}_D$ = –8.5 (*c* 0.47, MeOH). Therefore, the levorotatory enantiomer has the 2*R*,4*S*,5*S*,10*S*,13*S* absolute configuration.

Scheme 6. Total Synthesis of (–)-Cylindricine H



In summary, the first total synthesis of (–)-cylindricine H has been achieved by employing the tricyclic lactam **1** as the starting enantiomeric scaffold. The synthetic sequence includes as key steps the formation of the quaternary stereocenter by the insertion of an allyl substituent on an hemiaminal moiety and a series of highly stereoselective transformations for the incorporation of the C_4 acetoxy and C_2 butyl groups by synthetic manipulation of the amide functionality. To complete the synthesis, the pyrrolidine ring was closed by intramolecular opening of an epoxide. The synthesis of (–)-cylindricine H further illustrates the potential of phenylglycinol-derived tricyclic lactams for the assembly of complex natural products bearing the DHQ nucleus.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Complete experimental procedures and copies of ^{1}H and ^{13}C NMR spectra of all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

Mercedes Amat - *Laboratory of Organic Chemistry, Faculty of Pharmacy and Food Sciences, and Institute of Biomedicine (IBUB), University of Barcelona, 08028-Barcelona, Spain;* E-mail: amat@ub.edu

Authors

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Financial support from the MINECO/FEDER (project RTI2018-093974-B-I00) is gratefully acknowledged. Thanks are also due to the MINECO (Spain) for a fellowship to A.P., and the University of Barcelona for a fellowship to M.P.; R.G. is a Serra Húnter Fellow.

REFERENCES

(1) (a) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. Cylindricines A and B, Novel Alkaloids from the Ascidian Clavelina Cylindrica. *Tetrahedron* **1993**, *49*, 8645–8656. (b) Li, C.; Blackman, A. J. Cylindricines C-G, Perhydropyrrolo[2,1-*j*]quinolin-7-one Alkaloids from the Ascidian *Clavelina cylindrica*. *Aust. J. Chem*. **1994**, *47*, 1355–1361. (c) Li, C.; Blackman, A. J. Cylindricines H-K, Novel Alkaloids from the Ascidian *Clavelina cylindrica*. *Aust. J. Chem*. **1995**, *48*, 955–965.

(2) For reviews, see: (a) Schär, P.; Cren, S.; Renaud, P. Tricyclic Marine Alkaloids: Synthetic Approaches to Cylindricines, Lepadiformine, and Fasicularin. *Chimia* **2006**, *60*, 131–141. (b) Weinreb, S. M. Studies on Total Synthesis of the Cylindricine/Fasicularin/Lepadiformine Family of Tricyclic Marine Alkaloids. *Chem. Rev*. **2006**, *106*, 2531–2549. (c) Kaga, A.; Chiba, S. Synthesis of Tricyclic Marine Alkaloids, Cylindricines, Lepadiformines, Fasicularin, and Polycitorols: A Recent Update. *Synthesis* **2018**, 685–699.

(3) (a) Molander, G. A.; Rönn, M. Total Synthesis of (−)-Cylindricine C. *J. Org. Chem*. **1999**, *64*, 5183–5187. (b) Trost, B. M.; Rudd, M. T. Chemoselectivity of the Ruthenium-Catalyzed Hydrative Diyne Cyclization: Total Synthesis of (+)-Cylindricine C, D, and E. *Org. Lett*. **2003**, *5*, 4599–4602. (c) Arai, T.; Abe, H.; Aoyagi, S.; Kibayashi, C. Total Synthesis of (+)-cylindricine C. *Tetrahedron Lett*. **2004**, *45*, 5921–5924. (d) Canesi, S.; Bouchu, D.; Ciufolini, M. A. Fully Stereocontrolled Total Syntheses of (−)-Cylindricine C and (−)-2-Epicylindricine C: A Departure in Sulfonamide Chemistry. *Angew. Chem., Int. Ed*. **2004**, *43*, 4336–4338. (e) Liu, J.; Hsung, R. P.; Peters, S. D. Total Syntheses of (+)-Cylindricines C−E and (−)-Lepadiformine through a Common Intermediate Derived from an aza-Prins Cyclization and Wharton's Rearrangement. *Org. Lett*. **2004**, *6*, 3989–3992. (f) Abe, H.; S. Aoyagi, S.; Kibayashi, C. Total Synthesis of the Tricyclic Marine Alkaloids (−)-Lepadiformine, (+)-Cylindricine C, and (−)-Fasicularin via a Common Intermediate Formed by Formic Acid-Induced Intramolecular Conjugate Azaspirocyclization. *J. Am. Chem. Soc*. **2005**, *127*, 1473–1480. (g) Liu, J.; Swidorski, J. J.; Peters, S. D.; Hsung, R. P. An *N*-Acyliminium Cyclization Approach to a Total Synthesis of (+)-Cylindricine C. *J. Org. Chem*. **2005**, *70*, 3898–3902. (h) Wang, J.; Swidorski, J. J.; Sydorenko, N.; Hsung, R. P.; Coverdale, H. A.; Kuyava, J. M.; Liu, J. Aza-[3+3] Annulations. Part 6. Total Synthesis of Putative (−)-Lepadiformine and (−)-Cylindricine C. *Heterocycles* **2006**, *70*, 423–459. (i) Swidorski, J. J.; Wang, J.; Hsung, R. P. A Concise Total Synthesis of (−)-Cylindricine C through a Stereoselective Intramolecular Aza-[3+3] Annulation Strategy. *Org. Lett*. **2006**, *8*, 777–780. (j) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Sakuraba, S.; Ohshima; T.; Shibasaki, M. Short Synthesis of (+)-Cylindricine C by Using a Catalytic Asymmetric Michael Reaction with a Two-Center Organocatalyst. *Angew. Chem., Int. Ed*. **2006**, *45*, 4635–4637. (k) Mihara, H.; Shibuguchi, T.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. Short Synthesis of (+)-Cylindricine C and Formal Total Synthesis of (−)-Lepadiformine. *Heterocycles* **2007**, *72*, 421–438. (l) Pandey, G.; Janakiram, V. Aza-Quaternary Scaffolds from Selective Bond Cleavage of Bridgehead-Substituted 7-Azabicyclo[2.2.1]heptane: Total Synthesis of (+)-Cylindricines C–E and (−)-Lepadiformine A. *Chem. Eur. J*. **2015**, *21*, 13120–13126. (m) Hiraoka, S.; Matsumoto, T.; Matsuzaka, K.; Sato, T.; Chida, N. Approach to Fully Substituted Cyclic Nitrones from *N*-Hydroxylactam Derivatives: Development and Application to the Total Synthesis of Cylindricine C. *Angew. Chem., Int. Ed*. **2019**, *58*, 4381–4385. (n) Huang, Y.-H.; Lui, Z-J.; Huang, P.-Q. Enantioselective Total Syntheses of Marine Natural Products (+)-Cylindricines C, D, E and Their Diastereomers. *Org. Chem. Front*. **2022**, *9*, 58–63.

(4) Amat, M.; Ghirardi, E.; Navío, L.; Griera, R.; Llor, N.; Molins, E.; Bosch, J. Enantio- and Diastereoconvergent Cyclocondensation Reactions: Synthesis of Enantiopure *cis*-Decahydroquinolines. *Chem. Eur. J*. **2013**, *19*, 16044–16049.

(5) (a) Amat, M.; Griera, R.; Fabregat, R.; Molins, E.; Bosch, J. A Biomimetic Enantioselective Approach to the Decahydroquinoline Class of Dendrobatid Alkaloids. *Angew. Chem. Int. Ed.* **2008**, *47*, 3348–3351. (b) Piccichè, M.; Pinto, A.; Griera, R.; Bosch, J.; Amat, A. Enantioselective Total Synthesis of (+)-Gephyrotoxin 287C. *Org. Lett.* **2017**, *19*, 6654−6657.

(6) (a) Pinto, A; Griera, R.; Molins, E.; Fernández, I.; Bosch, J.; Amat, M. Access to Enantiopure 5-, 7-, and 5,7-Substituted *cis*-Decahydroquinolines: Enantioselective Synthesis of (−)-Cermizine B. *Org. Lett*. **2017**, *19*, 1714−1717. (b) Pinto, A.; Piccichè, M.; Griera, R.; Molins, E.; Bosch, J.; Amat, M. Studies on the Synthesis of Phlegmarine-Type Lycopodium Alkaloids: Enantioselective Synthesis of (−)-Cermizine B, (+)-Serratezomine E, and (+)-Luciduline. *J. Org. Chem*. **2018**, *83*, 8364−8375.

(7) (a) Amat, M.; Pinto, A.; Griera, R.; Bosch, J. Stereoselective Synthesis of (−)-Lepadins A-C. *Chem. Commun*. **2013**, *49*, 11032−11034. (b) Amat, M.; Pinto, A.; Griera, R.; Bosch, J. Enantioselective Synthesis of Lepadins A-D from a Phenylglycinol-Derived Hydroquinolone Lactam. *Chem. Eur. J*. **2015**, *21*, 12804−12808.

(8) Amat, M.; Bassas, O.; Llor, N.; Cantó, M.; Pérez, M.; Molins, E.; Bosch, J. Dynamic Kinetic Resolution and Desymmetrization Processes: A Straightforward Methodology for the Enantioselective Synthesis of Piperidines. *Chem. Eur. J*. **2006**, *12*, 7872–7881.

(9) (a) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. Total Synthesis of (+)-Halichlorine: An Inhibitor of VCAM-1 Expression. *Angew. Chem. Int. Ed.* **1999**, *38*, 3542–3545. See also (b) Lin, C. H.; Haadsma-Svensson, S. R.; Mccall, R. B.; Romero, A. G.; Darlington, W. H.; Ennis, M. D. Carboxamido-(1,2N)-carbocyclic-2-aminotetralin derivatives. WO92/20655A1, 1992.

(10) Ghirardi, E. Enantio- and Diastereoselective Cyclocondensation Reactions. Stereocontrolled Access to Azabicycles and Application to Natural Product Synthesis. Ph.D. Thesis, University of Barcelona, Barcelona, Spain, 2016.

(11) Aron, Z. D.; Ito, T.; May, T. L.; Overman, L. E.; Wang, J. Enantioselective Synthesis of Angularly Substituted 1-Azabicylic Rings: Coupled Dynamic Kinetic Epimerization and Chirality Transfer. *J. Org. Chem.* **2013**, *78*, 9929−9948.

(12) (a) Mun, S.; Lee, J.-E.; Yun, J. Copper-Catalyzed β-Boration of Acyclic α,β-Unsaturated Carbonyl Compounds: Rate Acceleration by Alcohol Additives. *Org. Lett*. **2006**, *8*, 4887–4889. (b) Lee, J.-E., Yun, J. Catalytic Asymmetric Boration of Acyclic α,β-Unsaturated Esters and Nitriles. *Angew. Chem. Int. Ed.* **2008**, *47*, 145–147.

(13) Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon: Oxford, 1983, p 221.

(14) For a review, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994**, *94*, 2483–2547.