Access to Enantiopure 5-, 7-, and 5,7-Substituted *cis*-Decahydroquinolines. Enantioselective Synthesis of (–)-Cermizine B

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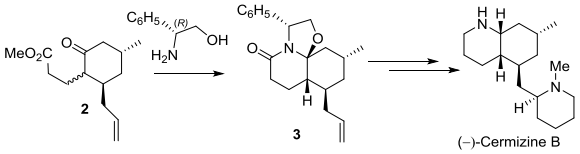
Supporting Information Placeholder



ABSTRACT: Stereoconvergent cyclocondensation reactions of (*R*)- or (*S*)-phenylglycinol with appropriately substituted cyclohexanone-based δ-keto esters are the key steps of short synthetic routes to enantiopure 5-, 7-, and 5,7-substituted *cis*-decahydroquinolines. The factors governing the stereoselectivity of the cyclocondensation are discussed. The potential of the methodology is illustrated by a protecting-group-free synthesis of the phlegmarine-type *Lycopodium* alkaloid (–)-cermizine B.

The decahydroquinoline (DHQ) ring system is present in hundreds of naturally occurring biologically active alkaloids, isolated not only from plant species but also from amphibians, arthropods, and marine organisms.[1] The structural and stereochemical diversity of these alkaloids makes them valuable targets for the development of unified synthetic strategies[2] and the validation of multipurpose building blocks.

In this context, using phenylglycinol-derived tricyclic lactams as chiral scaffolds, we have developed straightforward routes for the enantioselective synthesis of 5-, 6-, 8-, 2,5-, and 6,8-alkyl substituted *cis*-DHQs,[3] including the DHQ alkaloids pumiliotoxin C,[3a,c] lepadins A-D,[3f] and myrioxazine A.[3e]

We report herein the use of a new phenylglycinol-derived tricyclic lactam **3** as the key building block for the enantioselective synthesis of cermizine B,[4] a member of the small group of phlegmarine-type *Lycopodium* alkaloids,[5] which are characterized by a DHQ ring bearing a C-7 methyl substituent and a C-5 2-piperidylmethyl-based side chain (Figure 1). We also report a joint experimental-computational study carried out to understand the factors governing the stereoselectivity of the cyclocondensation reactions leading to **3** and related tricyclic lactams.

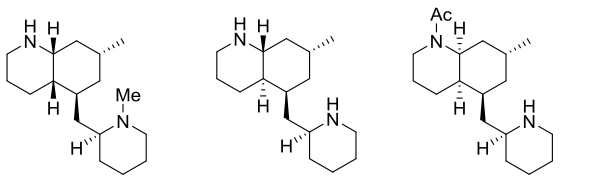
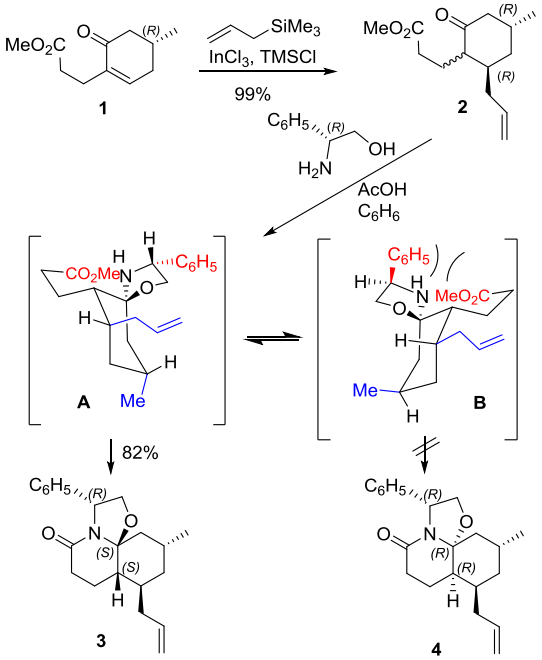


Figure 1. Representative phlegmarine-type *Lycopodium* alkaloids.

From a synthetic standpoint, phlegmarine-type alkaloids are among the least studied *Lycopodium* alkaloids, with only a limited number of enantioselective syntheses reported so far in both the *cis*-[6] and *trans*-DHQ[7] series.[8]

Tricyclic lactam **3**, bearing the appropriate absolute configuration for the synthesis of (–)-cermizine B, was prepared in a stereoconvergent manner as outlined in Scheme 1. The starting cyclohexenone-based δ-keto ester **1** was accessible in four steps from *R*-(+)-pulegone in approximately 70% overall yield on a multigram scale, as previously reported.[9] The $InCl_3$-catalyzed Sakurai reaction[10] of enone **1** with allyltrimethylsilane in the presence of trimethylsilyl chloride was highly diastereoselective, leading to *trans*-3,5-disubstituted cyclohexanone **2**[11] in nearly quantitative yield as a 1:1 mixture of C-2 epimers. Finally, heating a benzene solution of the above mixture of δ-keto esters and (*R*)-phenylglycinol in the presence of AcOH, using a Dean–Stark system, stereoselectively gave a single tricyclic *cis*-fused lactam **3** in 82% yield. This process involves the epimerization of the configurationally labile sterocenter α to the ketone group.

Scheme 1. Preparation of the Key Phenylglycinol-Derived Tricyclic Lactam 3

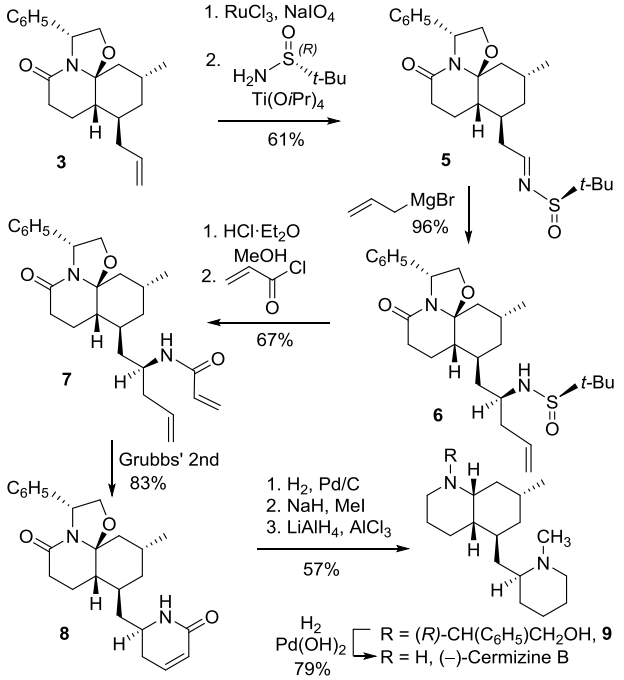


The stereoselectivity of the above cyclocondensation reaction was not unexpected[12] and can be rationalized by considering that the initially formed imines are in equilibrium with the corresponding enamines and four diastereoisomeric oxazolidines. The final irreversible lactamization occurs faster from oxazolidine **A**, which allows the ester group to approach the nitrogen atom from the less hindered face of the oxazolidine ring, *anti* to the phenyl, leading to *cis*-fused[13] lactam **3**. Formation of the alternative *cis*-fused lactam **4**, resulting from lactamization of oxazolidine **B**, was not observed. The absolute configuration of **3** was unambiguously established by X-ray crystallographic analysis.[14]

The allyl substituent at C-5 of the DHQ ring was used to stereoselectively assemble the C-5 2-(*S*)-piperidylmethyl moiety characteristic of (–)-cermizine B. A ruthenium catalyzed[15] oxidative cleavage of olefin **3**, followed by reaction of the resulting aldehyde with the chiral auxiliary (*R*)-(+)-*tert*-butanesulfinamide afforded *N*-sulfinyl imine **5** in 61% yield[16] (Scheme 2). A subsequent allylation with allylmagnesium bromide stereoselectively[17] provided sulfinamide **6** as a single stereoisomer, which incorporates a newly created stereogenic center having the required *S*-configuration. Cleavage of the chiral auxiliary by acid methanolysis, followed by reaction of the resulting primary α-branched amine with acryloyl chloride gave diene **7**, which underwent an RCM reaction to afford dihydropyridone **8** in excellent yield.

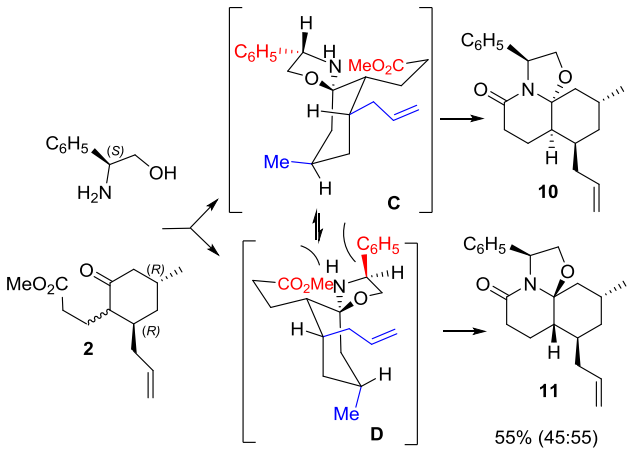
The synthesis of (–)-cermizine B was completed by conventional transformations involving catalytic hydrogenation of **8**, lactam methylation, alane reduction, which brought about the reduction of the two lactam carbonyls and the reductive opening of the oxazolidine ring, and final debenzylation by catalytic hydrogenation of the resulting *cis*-DHQ **9**. Our synthetic cermizine B showed NMR data and a sign of specific rotation [–16.0 (*c* 0.29, MeOH); Lit[4] –2 (*c* 0.6, MeOH)] coincident with those reported[4,18] for the natural product.

Scheme 2. Enantioselective Synthesis of (–)-Cermizine B



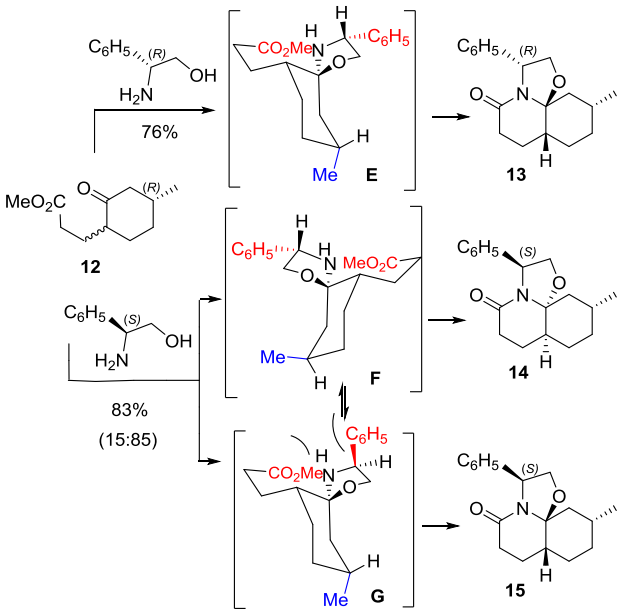
At this point we reasoned that a similar reaction sequence starting from (*S*)- instead of (*R*)-phenylglycinol would provide a synthetic entry to (+)-serratezomine E, a phlegmarine-type alkaloid with a *cis*-fusion opposite to that of cermizine B, via tricyclic lactam **10** (Scheme 3). However, surprisingly, cyclocondensation of δ-keto esters **2** with (*S*)-phenylglycinol gave a nearly equimolecular mixture of diastereoisomeric lactams **10** and **11** (45:55 ratio). The irreversible lactamization takes place not only from the expected oxazolidine **C** via a chair-like transition state that avoids repulsive interactions with the phenyl substituent, but also from **D**, which suffers from such interactions. Both **C** and **D** incorporate an axial substituent on the cyclohexane ring.[19]

Scheme 3. Cyclocondensation Reaction of δ-Keto Esters 2 with (*S*)-Phenylglycinol

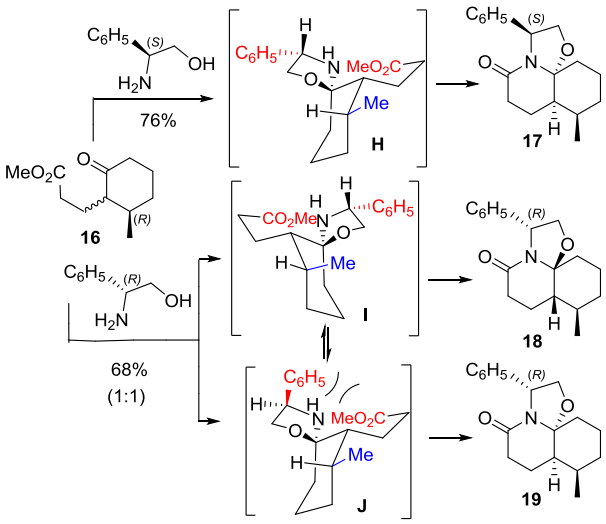


To understand the effect of the substituents at the C-5 and C-7 positions (DHQ numbering) in the above cyclocondensation reactions, we studied similar reactions from (*R*)- and (*S*)-phenylglycinol and model keto esters **12**[20] and **16**.[21] The results are shown in Schemes 4 and 5.

Scheme 4. Cyclocondensation Reaction of δ-Keto Esters 12 with (*R*)- and (*S*)-Phenylglycinol



Scheme 5. Cyclocondensation Reaction of δ-Keto Esters 16 with (*R*)- and (*S*)-Phenylglycinol

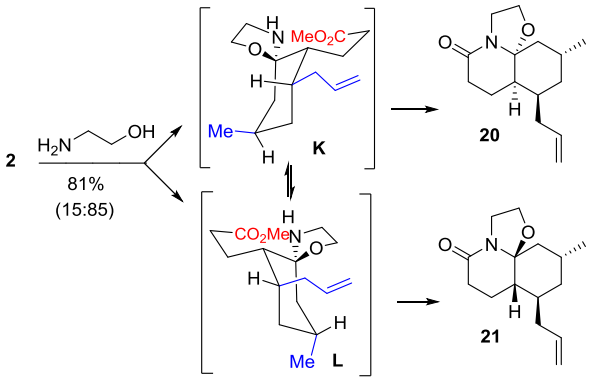


Similar to the above cyclocondensations from **2**, the reaction of **12** with (*R*)-phenylglycinol stereoselectively gave a single tricyclic lactam **13**, via oxazolidine **E**, whereas the reaction with (*S*)-phenylglycinol was not stereoselective, affording a 15:85 mixture of lactams **14** and **15**. In contrast, δ-keto ester **16** led to a single tricyclic lactam **17** by reaction with (*S*)-phenylglycinol and afforded a nearly equimolecular mixture of lactams **18** and **19** by reaction with (*R*)-phenylglycinol.

The stereoselective generation of lactams **13** and **17** can be accounted for by considering the easy lactamization of the respective oxazolidine intermediates **E** and **H** (equatorial methyl group and no interactions with the phenyl substituent during the ring closure). On the other hand, the formation of lactam **15** as the major product in the cyclocondensation of **12** with (*S*)-phenylglycinol (**14**/**15** 15:85 ratio) simply reflects the strong destabilizing interactions of the axial methyl substituent in the intermediate oxazolidine **F**, precursor of **14**. In the light of this result, the 1:1 ratio for lactams **18** and **19** in the cyclocondensation of **16** with (*R*)-phenylglycinol (Scheme 5) is quite striking, suggesting that oxazolidine **J** suffers from an additional destabilizing effect.

To definitively clarify the influence of the C-5 and C-7 substituents (DHQ numbering) in the above cyclocondensation reactions, we also studied the cyclocondensation δ-keto ester **2** (1:1 mixture of C-2 epimers) with 2-aminoethanol, a simple β-amino alcohol lacking the phenyl substituent of the phenylglycinol moiety. A 15:85 mixture of tricyclic lactams **20** and **21** was obtained in 81% yield (Scheme 6).

Scheme 6. Cyclocondensation Reaction of δ-Keto Ester 2 with 2-Aminoethanol

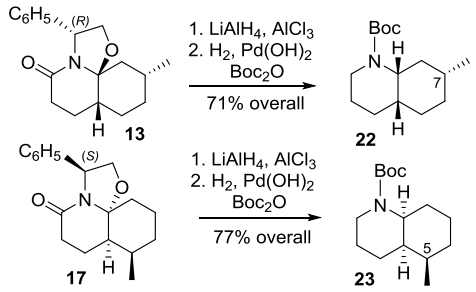


A rationale for this result and those of all the above cyclocondensations is that, although both oxazolidine intermediates **K** and **L** incorporate an axial methyl or allyl substituent on the cyclohexane ring, **K** also suffers from repulsive *gauche* interactions between the equatorial allyl substituent and the propionate chain. This hypothesis is supported by theoretical calculations, which confirm that the protonated intermediate **L**·H$^+$, the species from which the cyclization occurs, is indeed 3.2 Kcal/mol more stable than the analogous **K**·H$^+$ intermediate due to the occurrence of such destabilizing interactions.[22]

In summary, the stereochemical outcome of the cyclocondensations reported herein depends on the repulsive interactions in the intermediate oxazolidines that undergo irreversible lactamization. These interactions are mainly caused by i) the approach of the ester group to the nitrogen, *syn* with respect to the phenyl substituent, during the lactamization step; ii) the presence of axial substituents on the cyclohexane ring; and iii) the repulsive *gauche* interaction between the equatorial C-5 substituent (DHQ numbering) and the propionate chain.

Finally, to further illustrate the synthetic potential of the above cyclocondensation reactions leading to substituted tricyclic lactams, enantiopure lactams **13** and **17** were converted in excellent yields to the respective 7- and 5-substituted *cis*-DHQs **22** and **23** by the two-step sequence depicted in Scheme 7.

Scheme 7. Access to Enantiopure 5- and 7-Substituted *cis*-Decahydroquinolines



In conclusion, we have developed straightforward routes (only three synthetic steps) to enantiopure 5-, 7-, and 5,7-substituted *cis*-DHQs by cyclocondensation of stereoisomeric mixtures of cyclohexanone-derived δ-keto esters with (*R*) and (*S*)-phenylglycinol, which acts as a chiral latent form of ammonia. Understanding the factors that govern the stereoselectivity of these reactions will allow the design of related stereocontrolled cyclocondensation reactions leading to enantiopure *cis*-DHQs with different substitution and stereochemical patterns.

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(12) The same stereochemical outcome was observed in cyclocondensation reactions leading to related tricyclic phenylglycinol-derived lactams: see ref 3.

(13) Formation of *trans*-fused lactams is precluded on steric grounds.

(14) CCDC 1533231 contains the supplementary crystallographic data for compound **3**. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(18) It has been pointed out[4] that the reported $[\alpha]_D$ value of cermizine B "is not reliable due to small amount of sample and small value of optical rotation."

(19) Interestingly, cyclocondensation of 4-methyl-5-nitromethyl-2-oxocyclopentaneacetic acid (a γ-keto acid) with (*R*)- and (*S*)-phenylglycinol gave in both cases the expected tricyclic (5,5,5-membered) lactams as single products: Deprez-Poulain, R.; Willand, N.; Boutillon, C.; Nowogrocki, G.; Azaroual, N.; Deprez, B. *Tetrahedron Lett.* **2004**, *45*, 5287.

(20) Keto ester **12** (1:1 mixture of diastereoisomers) was prepared by catalytic hydrogenation (PtO_2) of cyclohexenone **1**.

(21) Keto ester **16** (2:1 mixture of diastereoisomers) was prepared in three steps from (*R*)-(+)-pulegone: a) $CH_2{=}N^+Me_2Cl^-$, acetonitrile; b) $CH_2(CO_2Et)_2$, NaOH, toluene, reflux; then AcOH-HCl (2:1), reflux; c) TMSCl, MeOH.

(22) Calculations were carried out at the PCM(benzene)-B3LYP-D3/6-31+G(d,p) level. See the Supporting Information for details.

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