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Exceedingly Concise and Elegant Synthesis of (+)-Paniculatine, (−)-Magellanine, and (+)-Magellaninone

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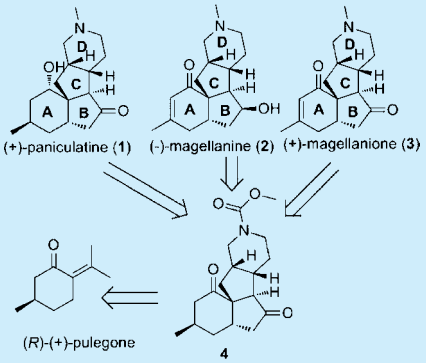
Supporting Information

ABSTRACT: Starting from inexpensive (+)-pulegone as the chiral building block, a highly convergent synthesis of the unusual diquinane-based structures of (+)-paniculatine (**1**), (−)-magellanine (**2**), and (+)-magellaninone (**3**), has been achieved. This approach is based upon a tandem acylation−alkylation of ketoester **8** and palladium-catalyzed olefin insertion, oxidation, and hydrogenation for construction of the tetracyclic framework. This exceedingly concise strategy, requiring only 12−14 steps, is the shortest to date.



The *Lycopodium* alkaloids are a family of skeletally diverse natural products that have continued to attract much synthetic interest due to their polycyclic architecture and useful biological activity.[1] The unusual diquinane-based structure of (+)-paniculatine (**1**),[2a] (−)-magellanine (**2**),[2b] and (+)-magellaninone (**3**),[2c] which are unique members of *Lycopodium* alkaloids, represents a challenging vehicle to explore the development of efficient methodology for the stereocontrolled construction of the complete diquinane-based tetracyclic framework and the direct installation of the five to seven stereogenic centers of these ring systems. Several synthetic approaches toward construction of the requisite tetracyclic skeleton have been reported. In 1993, enantioselective total syntheses of both (−)-magellanine and (+)-magellaninone via a Prins−pinacol rearrangement was successfully completed over 25−26 steps by Overman.[3] In the same year, a 20-step racemic synthesis of magellanine and magellaninone based upon Michael−Michael addition was accomplished by Paquette et al.[4] In addition, the first 26-step asymmetric synthesis of (+)-paniculatine from (*R*)-(+)-pulegone was achieved by Sha et al. in 1999 via a novel application of tandem radical cyclization to produce the angularly fused tricyclic skeleton.[5] In 2002, a 16-step synthesis of (±)-magellanine by Liao demonstrated the value of the oxa-di-π-methane rearrangement for construction of the linear triquinane framework.[6] By employing the Pauson−Khand reaction of an enyne for the construction of the bicycle[4.3.0] framework, asymmetric syntheses of (+)-paniculatine, (−)-magellanine, and (+)-magellaninone in 43−45 steps from diethyl L-tartrate were demonstrated by the group of Mukai in 2007.[7a] Very recently, Yang and co-workers reported the use of site-specific and stereoselective aldol cyclization in the collective total synthesis of tetracyclic diquinane *Lycopodium* alkaloids in 25−28 steps from (*R*)-(+)-pulegone.[7b] Given the background, the development of exceedingly concise and convergent synthetic strategies to the three *Lycopodium* alkaloids (+)-paniculatine, (−)-magellanine, and (+)-magellaninone remains an attractive challenge.

Herein, we report a new synthetic strategy that leads from an inexpensive (*R*)-(+)-pulegone-derived enone **9**[8] to the diketocarbamate **4**, a convenient precursor to (+)-paniculatine, (−)-magellanine, and (+)-magellaninone.

Scheme 1 outlines, in retrosynthetic format, our overall plan for construction of the required tetracyclic diketocarbamate **4** from (*R*)-(+)-pulegone. We envisioned the diketocarbamate **4** to be derived from the Pd-catalyzed intramolecular olefin insertion of keto−enol triflate **5**, whose connection to bicyclic diketone **6** could be recognized through standard functional group manipulations. The origins of **6** were then traced to ketoester **8** through tandem intramolecular acylation/intermolecular alkylation. Finally, ketoester **8** was expected to arise from enone **9** through a conjugate addition of a functionalized zinc−copper reagent.

According to the synthetic blueprint, the synthesis of **8** began from chiral enone **9** (Scheme 2). Thus, 1,4-addition of zinc homoenolate to enone **9** under copper-catalyzed conditions ($CuBr{\cdot}SMe_2$/TMSCl/HMPA)[9] led smoothly to the desired ketoester **8** in 85% yield with complete stereocontrol. To incorporate the B and D rings into **8**, with concomitant stereocontrolled construction of the quaternary center, application of a base-promoted intramolecular cyclization and an intermolecular alkylation with the ketoester **8** were attempted. Gratifyingly, exposure of **8** to *t*-BuOK in THF at 0 °C for 1 h followed by the addition of DBU and 3-

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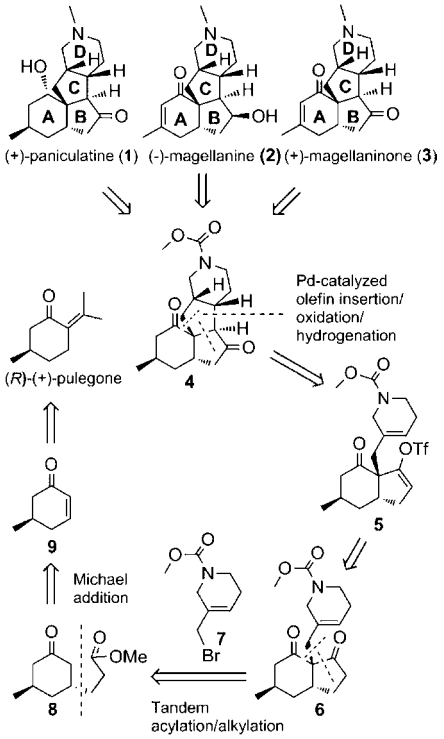
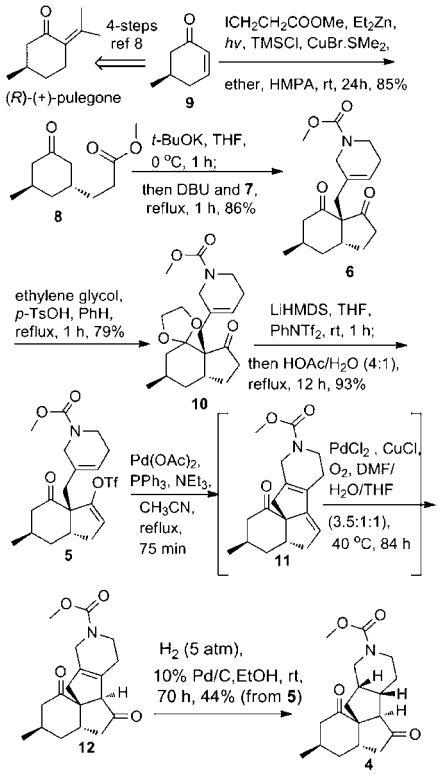
Scheme 1. Retrosynthetic analysis of (+) - paniculatine, (−)-magellanine, and (+)-magellaninone



Scheme 2. Synthesis of Diketocarbamate 4



pyridinemethanol-derived allyl bromide **7**,[10] and heating at reflux for 1 h smoothly and cleanly effected the desired cyclization and alkylation to afford the desired bicyclic diketone **6** in 86% yield. The quaternary carbon center was correctly installed by this remarkable transformation. The desired stereochemical outcome of this tandem conjugate addition/alkylation sequence was achieved as anticipated on steric grounds. The next object was the forging of the final carbocyclic C ring within the skeleton of **6**. To accomplish this goal, an intramolecular Heck was envisaged. Incorporation of the final C ring was initiated by chemoselective ketalization ($HOCH_2CH_2OH/H^+$), which produced a single diastereomeric keto ketal **10** in 79% yield. Conversion of **10** into its enol triflate ($LiHMDS/PhNTf_2$) and removal of the dioxolane group (80% HOAc) could be accomplished in one pot to give keto−enol triflate **5** in 93% yield. The critical Pd-promoted intramolecular olefin insertion was effected by exposing **5** to 0.09 equiv of $Pd(OAc)_2$ and 0.26 equiv of PPh_3 in CH_3CN/NEt_3 and gave the tetracyclic dienone **11** in 82% yield. With dienone **11** in hand, we began to investigate the challenging chemoselective oxidation of the diene with concomitant stereocontrolled construction of the tertiary center. Through an extensive screening of reaction conditions, we found that the desired enediketone **12** could be generated in 55% yield by the treatment of dienone **11** with $PdCl_2/CuCl/O_2$ in $DMF/H_2O/THF$ at 40 °C for 84 h.[11] Subsequent hydrogenation of the alkene that remained with H_2 (5 atm)/10% Pd/C in EtOH provided the desired diketocarbamate **4** in 86% yield. The configuration of this saturated diketocarbamate **4** was confirmed by single-crystal X-ray analysis (see the Supporting Information). This overall sequence has allowed diketocarbamate **4** to be prepared in enantiopure fashion in 39% overall yield from **5**. A more convenient operation took keto−enol triflate **5** through the three-step without purification of any intermediates to deliver the diketocarbamate **4** in 44% overall yield, which is identical to what was obtained when each step began with purified material.

The ready accessibility to **4** by the preceding protocol has set the stage for completion of the synthesis of (+)-paniculatine (**1**) (Scheme 3). Thus, chemoselective silylation of one of the two ketones in **4** with TBSCl/NaH in THF at 0−25 °C provided the desired silyl enol ether **13** in 92% yield. After careful optimization of the reduction conditions, we were pleased to find that treatment of **13** with L-Selectride in THF at −78 to +25 °C for 8 h, followed by addition of DIBAL-H at 0 °C and stirring for 1 h and then addition of 2 N HCl and stirring for 1 h, afforded an 85% yield of (+)-paniculatine (**1**), $[\alpha]^{25}_D = +77.38$ (*c* 0.88, $CHCl_3$), whose physical properties are identical to those reported earlier,[6] and its structure was secured by single-crystal X-ray analysis. The excellent diastereocontrolled introduction of the last stereogenic center on the A ring with >13:1 diastereoselectivity is noteworthy.

The synthetic route described above makes use of novel approaches to the construction of the tetracyclic framework and for the introduction of seven stereogenic centers. The asymmetric synthesis requires 12 steps from commercially available (+)-pulegone to give (+)-paniculatine in ∼8.2% overall yield.

This convergent sequence offers an exceedingly concise and elegant approach to the tetracyclic framework of this family of alkaloids which share a common diquinane core. To demonstrate the versatility of this convergent strategy, we were able to access both (−)-magellanine (**2**) and (+)-magellaninone (**3**). All that now remained to reach these targets was the functionalization of the A and B rings. Fortunately, exposing **4** to L-Selectride in THF at −78 °C for 6 h cleanly effected the desired chemoselective reduction of the less hindered ketone in **4** to give ketocarbamate **14** in 96% yield

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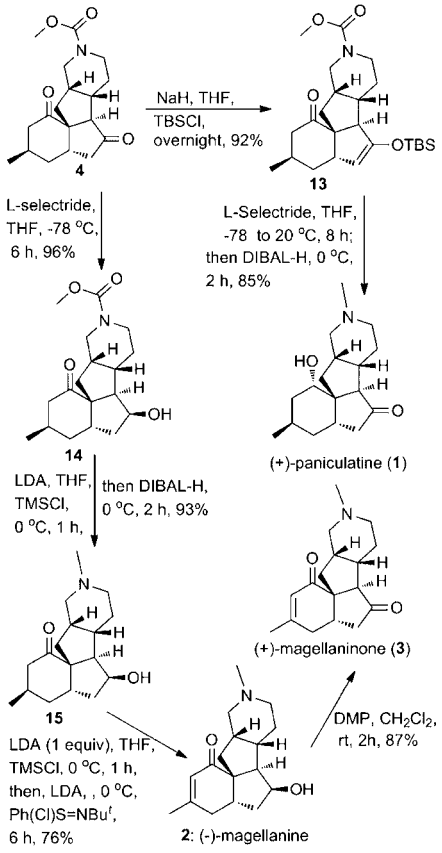
Scheme 3. Synthesis of (+)-paniculatine 1, (−)-magellanine 2, and (+)-magellaninone 3



with complete diastereoselectivity, and its structure was again secured by single-crystal X-ray analysis. Treatment of **14** with LDA (2 equiv) in THF at 0 °C followed by the addition of TMSCl (2 equiv) and DIBAL-H and stirring for 1 h, and then addition of 2 N HCl and stirring for an additional 1 h, cleanly effected the desired reduction of the ketocarbamate to an aminoketone to afford hydroxyketone **15** in 93% yield. Introduction of the remaining C = C double bond was realized via dehydrogenation of ketone with *N-tert*-butylphenylsulfinimidoyl chloride.[12] Exposing **15** with LDA (1 equiv) in THF at 0 °C followed by the addition of TMSCl and stirring for 1 h and then addition of LDA and *N-tert*-butyl phenylsulfinimidoyl chloride[12] at 0 °C resulted in efficient formation of the desired enone to furnish 76% yield of (−)-magellanine (**2**), whose spectral properties are in full agreement with those of the natural product.[3−5] Oxidation of the hydroxyl group in **2** with DMP at room temperature provided (+)-magellaninone (**3**) in 87% yield. The asymmetric synthesis of (−)-magellanine and (+)-magellaninone requires 13 and 14 steps, respectively.

In summary, an exceedingly concise and elegant synthesis of the advanced intermediate **4** en route to the three *Lycopodium* alkaloids (+)-paniculatine, (−)-magellanine, and (+)-magellaninone has been accomplished in 12−14 steps by using (+)-pulegone as an inexpensive chiral starting material. The asymmetric synthesis is the shortest to date. The most striking maneuver in this synthesis is the construction of tetracycle **4** by combining three-component coupling and palladium-mediated olefin reactions. This efficient and flexible entry should offer opportunities for the construction of many other polycycle analogues for chemical biology investigations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01975.

Experimental procedures and characterization data for all reactions and products, including ^{1}H and ^{13}C NMR spectra (PDF)
X-ray data for compound **1** (CIF)
X-ray data for compound **4** (CIF)
X-ray data for compound **14** (CIF)

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Notes

The authors declare no competing financial interest.

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