Organic LETTERS

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Collective Total Synthesis of Tetracyclic Diquinane *Lycopodium* Alkaloids (+)-Paniculatine, (−)-Magellanine, (+)-Magellaninone and Analogues Thereof

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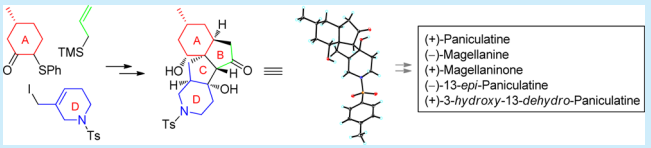
Supporting Information

ABSTRACT: The collective total synthesis of tetracyclic diquinane *Lycopodium* alkaloids, (+)-paniculatine, (−)-magellanine, (+)-magellaninone, and two analogues (−)-13-*epi*-paniculatine and (+)-3-hydroxyl-13-dehydro-paniculatine, has been accomplished. By logic-guided addition of a strategically useful hydroxyl group at C-3 of paniculatine, the formidable tetracyclic core was rapidly synthesized utilizing a site-specific and stereoselective aldol cyclization, thus making the ABD → ABCD tetracyclic approach to diquinane *Lycopodium* alkaloids attainable for the first time.



Lycopodium alkaloids have recently received much attention due to their diverse skeletal features and broad ranging biological activities.[1] In this context, numerous innovations in synthetic strategies and tactics have been introduced in a cornucopia of reports of total synthesis.[2] In contrast to the well investigated fawcettimine type,[3] tetracyclic diquinane *Lycopodium* alkaloids still represent a formidable synthetic challenge owing to the unusually compacted polycyclic framework that bears up to six contiguous stereocenters, most of which, including an all-carbon quaternary, around a diquinane core (rings B, C) (Figure 1).

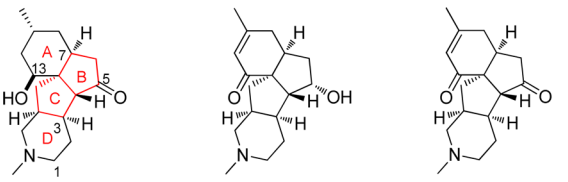


Figure 1. Tetracyclic diquinane *Lycopodium* alkaloids.

Tetracyclic diquinane *Lycopodium* alkaloids usually refer to the alkaloids of (+)-paniculatine, (−)-magellanine, and (+)-magellaninone which were isolated by Castillo et al. in the 1970s.[4] Since their isolation, extensive synthetic efforts have been made to conquer them.[5,6] In the known successful total synthesis reports,[5] as shown in Figure 2, synthetic strategies of the challenging tetracyclic core are typified by the liner construction of ABC → ABCD, and the basic piperidine D ring was formed either by oxidative cleavage of cyclopentene and then insertion of a N-atom (Overman,[5a] Liao,[5e] and Mukai[5g]) or by cyclization between a N-containing branch and another carbogenic side chain (Paquette,[5b,c] Sha,[5d] Ishizaki[5f]). The late-stage installation

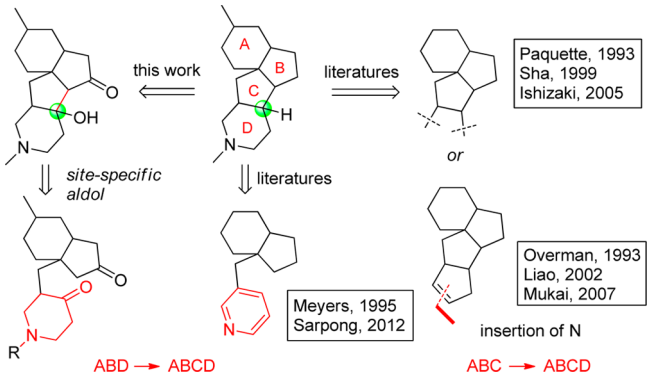


Figure 2. Strategies comparison for the ABCD tetracyclic formation.

of the D ring was often adopted because of the difficulties in the construction of the complex framework and controlling the highly basic tertiary amine group of these alkaloids. In recognition of this challenge, other groups pursued an alternative disconnection strategy. Two reports regarding the tetracyclic formation with a preinstalled D ring, namely ABD → ABCD, were published first by Meyers[6c] in 1995 and then Sarpong[6e] in 2012, both using pyridine as the D ring surrogate. Given the troubles encountered in the further functionalization, the core structures rather than natural products have been finished so far. Therefore, development of an unconventional ABD → ABCD approach to complete the tetracyclic diquinane *Lycopodium* is still an unsolved challenge. Here, we present a successful solution to this convergent ABD → ABCD formation, which was guided by the logic of retrosynthetic analysis producing the greatest

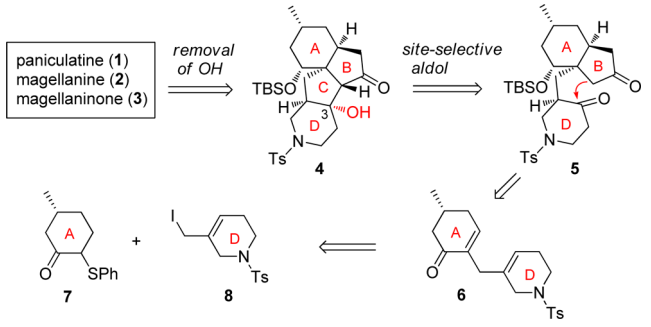
Received: September 10, 2014

   dx.doi.org/10.1021/ol502679v | *Org. Lett.* XXXX, XXX, XXX−XXX

molecular simplification, and culminating in the collective total synthesis of *Lycopodium* alkaloids (+)-paniculatine, (−)-magellanine, (+)-magellaninone, and two analogues, (−)-13-*epi*-paniculatine, (+)-3-hydroxyl-13-dehydro-paniculatine.

To simplify the complexity, the intelligent selection of transformations is of utmost importance.[7] After an evolution of retrosynthetic thinking, the derivative of C-3 hydroxyl paniculatine **4** was finally singled out to be the intermediate precursor of the tetracyclic diquinane alkaloids (in Scheme 1).

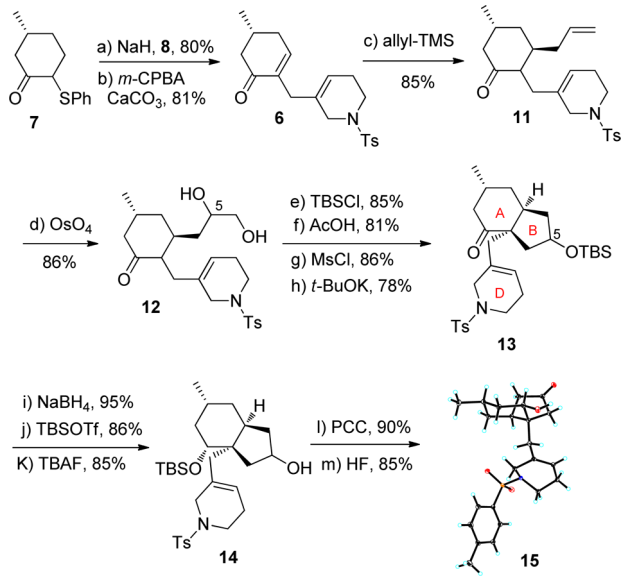
Scheme 1. Retrosynthetic Analysis of Tetracyclic Diquinane *Lycopodium* Alkaloids



Adding an extra hydroxyl group at C-3 is strategically useful, because it not only could be easily removed later, delivering the desired diquinane tetracycle, but also can simplify and accelerate the retrosynthetic disconnection of the targets by enlisting a site-specific and stereoselective[8] aldol cyclization of two carbonyl groups, which is the essence of our new ABD → ABCD strategy (Figure 2). The ABD tricyclic backbone **5** was in turn assembled by the annulation of the B ring into AD ring system **6**, utilizing the enone functionality of the A ring. Ultimately, the AD ring was stitched convergently from two readily available starting materials, thioether **7**[9] and allylic iodide **8**.

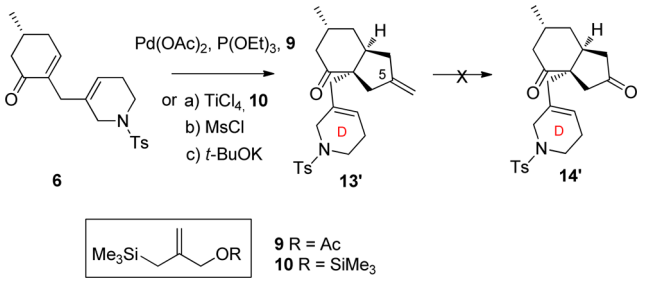
Our synthesis commenced with the AD ring formation (Scheme 2). Known **7** was alkylated with **8** (prepared from commercial arecoline; see the Supporting Information (SI)) thermodynamically. The product was oxidized with *m*-CPBA, and the resulting sulfoxide was subjected to elimination,[9] furnishing AD bicyclic cyclohexenone **6**. The annulation of the B ring into the AD bicyclic system, exploiting the chemistry of the enone functionality of cyclohexenone, was not trivial. Pd-catalyzed [3 + 2] trimethylenemethane **9** cycloaddition, developed by Trost,[10] was initially attempted and found extremely sluggish (Scheme 3). Using bisliane **10** under Lewis acid conditions,[11] a Sakurai reaction product (not shown) was obtained and the intermediate was advanced to close the B ring, furnishing the ABD tricyclic framework **13′** with a methylene group at C-5 that required cleavage. Unfortunately, in that case, the ensuing oxidative cleavage predominately occurred in the D ring's internal double bond. That problem was circumvented by using allyltrimethylsilane. The allylic group was selectively attached to cyclohexenone **6**, affording **11** which was selectively oxidized with dihydroxylation, giving a mixture of inconsequential ca. 1:1 isomeric diol **12** at C-5 (Scheme 2). To form the B ring, the primary alcohol should be converted into a leaving group for cyclization of an intramolecular alkylation. To this end, a practical procedure including bis-silylation, desilylation, mesylation, and alkylation was enlisted uneventfully to provide an inseparable ABD tricycle **13**. This cyclization to form the B ring is stereospecific, leading to a cis-fused AB ring system.[12]

Scheme 2. Synthesis of ABD Tricyclic Framework[a]



[a]Reagent and conditions: (a) NaH, DMF, **8**, rt, 80%; (b) *m*-CPBA, DCM, −78 °C to rt; $CaCO_3$, toluene, reflux, 81%; (c) $TiCl_4$, allyl-TMS, DCM, −78 °C to rt, 85%; (d) OsO_4, NMO, acetone/THF/*t*-BuOH/H_2O, 86%; (e) TBSCl, imidazole, DMF, rt, 85%; (f) AcOH/H_2O/THF, 70%, or 81% brsm; (g) MsCl, 4-DMAP, DCM, rt, 86%; (h) *t*-BuOK, THF, rt, 78%; (i) $NaBH_4$, MeOH, 0 °C, 95%; (j) TBSOTf, Et_3N, DCM, 0 °C, 86%; (k) TBAF, THF, rt, 85%; (l) PCC, Celite, rt, 90%; (m) HF·Py, THF, rt, 85%.

Scheme 3. Attempted Synthesis of ABD via [3 + 2] Cycloaddition

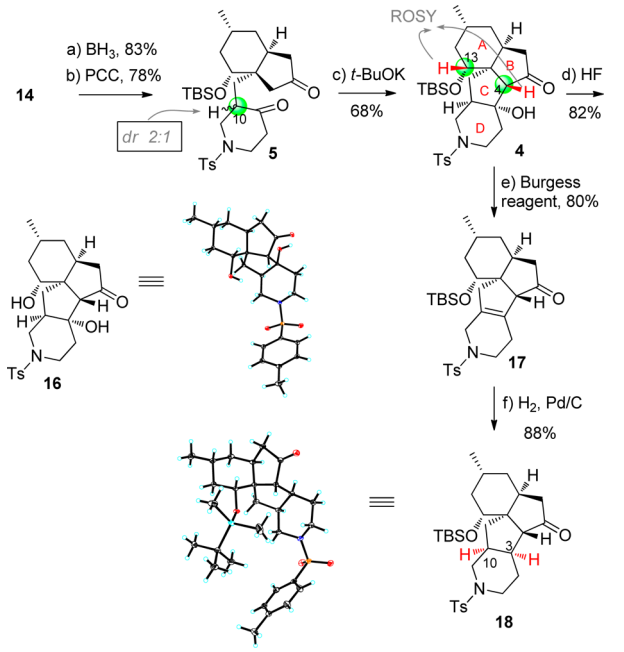


Therefore, **13** is still a pair of inconsequential isomers at the C-5, but both with the desired quaternary stereocenter at C-12. Considering that cyclohexanone would interfere with the upcoming pivotal aldol cyclization during ABD → ABCD, reduction of the cyclohexanone with $NaBH_4$ was necessary, and it provided a completely α-selective secondary alcohol that was protected as the TBS ether. Due to the steric difference, the sec-TBS ether at C-5 is much easier to remove. Then selective desilylation with TBAF afforded tricyclic alcohol **14**. Oxidation of **14** and removal of TBS provided a crystalline compound **15**, which was subjected to X-ray analysis. At this point, the complete structure of the ABD tricycle with four stereocenters was unequivocally confirmed.

To prepare the aldol cyclization precursor diketone **5**, hydroboration−oxidation of alkene **14** and further oxidation of the two hydroxyl groups into diketone were employed (Scheme 4). Homogenous **5** was difficult to acquire presumably due to incomplete facial selectivity of hydroboration or facile epimerization of the α-position of the D-ring ketone, yielding a ca. 2:1 epimeric diketone mixture at C-10. With diketone in hand, the

dx.doi.org/10.1021/ol502679v | *Org. Lett.* XXXX, XXX, XXX−XXX

Scheme 4. Synthesis of ABCD Tetracyclic Diquinane Core[a]

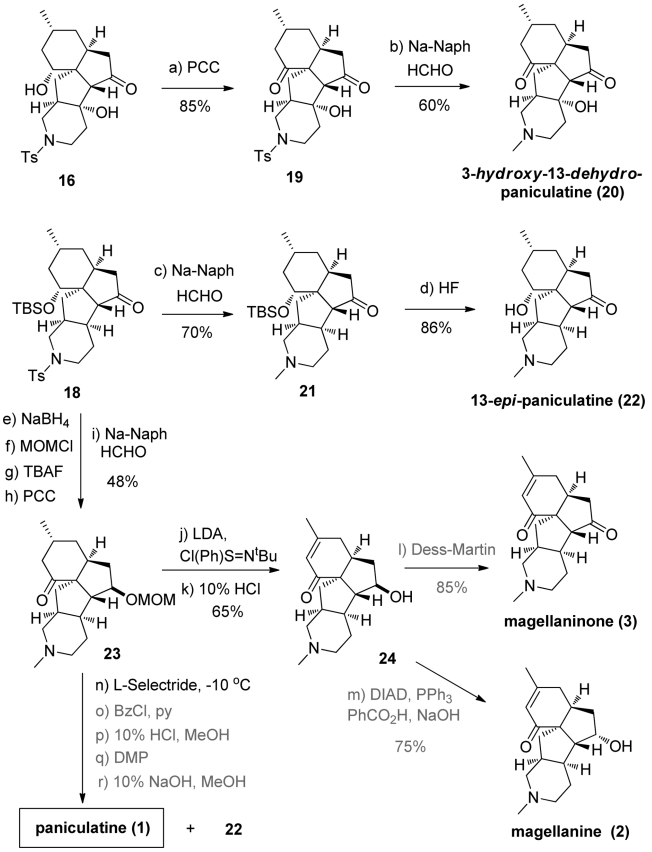


[a]Reagent and conditions: (a) $BH_3{\cdot}Me_2S$, THF, −5 °C, 3 days, 83%; (b) PCC, 4 Å M.S., DCM, rt, 78%; (c) *t*-BuOK, toluene, 0 °C, 68%; (d) HF·Py, THF, rt, 82%; (e) Burgess reagent, toluene, 4 Å M.S., 80 °C, 80%; (f) H_2, Pd/C (10%), EtOAc, rt, 88%.

stage was set for the most critical intramolecular aldol process. Gratifyingly, after treatment of **5** with potassium *tert*-butoxide in toluene, a smooth aldol cyclization occurred and yielded the ABCD tetracycle **4** with the anticipated site- and stereoselectivities. The isolated 68% yield is good enough to advance our synthesis.[13] The newly formed C-4 stereocenter was assigned according to the apparent ROSY signal correlation with the methine at C-13. More importantly, after removal of the TBS group, a crystalline compound **16** was grown and subjected to X-ray analysis, which gave a clear-cut validation of the ABCD tetracyclic system. This result has constituted, for the first time, a compound with the complete skeleton of tetracyclic diquinane through an ABD → ABCD synthetic approach. According to our collective synthesis proposal,[14] removal of the C-3 hydroxyl group was pursued. Deoxygenation through Barton−McCombie radical reaction[15] was impeded because the thiocarbonyl intermediate could not be formed in such a highly congested environment. Luckily, dehydration of **4** with the Burgess reagent[16] gave a sole product as tetrasubstituted alkene **17** in 80% yield. **17** could be smoothly saturated via hydrogenation,[6c] yielding a cis-fused tetracyclic diquinane **18**. Pleasingly, **18** is a crystalline compound whose complex stereochemistry around the diquinane core was confirmed again via X-ray single crystal analysis. The highly facial selectivity of hydrogenation probably attributed to the shielding effect to the top-side exerted by the bulking TBS group and bowl-shaped conformation of the substrate as well, leading to bottom-side approach.[17] So far, the most striking structural elements of tetracyclic diquinane *Lycopodium* alkaloids, except the stereochemistry of C-13 and *N*-methyl group, have been established.

To continue our total synthesis odyssey, as shown in Scheme 5, the tetracycle **16** was oxidized with PCC and deprotection of *p*-toluenesulfonamide followed by in situ *N*-methylation was executed, furnishing 3-hydroxy-13-dehydro-paniculatine (**20**).

Scheme 5. Collective Synthesis of Tetracyclic Diquinane *Lycopodium* Alkaloids[a]



[a]Reagent and conditions: (a) PCC, 4 Å M.S., DCM, rt, 85%; (b) Na-Naph, HCHO, $NaBH_3CN$, overnight, 60%; (c) Na-Naph, HCHO, $NaBH_3CN$, overnight, 70%; (d) HF·Py, CH_3CN/THF/acetone (1:1:1), rt, 86%; (e) $NaBH_4$, EtOH, 0 °C, 99%; (f) MOMCl, iPr_2NEt, rt, 96%; (g) TBAF, THF, 70 °C, 88%; (h) PCC, 4 Å M.S., DCM, rt, 92%; (i) Na-Naph, HCHO, $NaBH_3CN$, overnight, 62%; (j) LDA, THF, −20 °C, 1 h, Cl(Ph)S═N^{t}Bu, HMPA, −20 → 0 °C; (k) 10% HCl, MeOH, 65% 2 steps; (n) L-Selectride, THF, −10 °C.

Similarly, after TBS protected tetracycle **18** was subjected to in situ *N*-methylation and desilylation with hydrogen fluoride pyridine, 13-*epi*-paniculatine (**22**) was obtained smoothly. Tetracycle **18** was reduced with $NaBH_4$ to selectively afford sec-alcohol which was immediately protected with a MOM ether. After subjecting MOM ether to TBAF promoted desilylation of TBS and then oxidation of the new hydroxyl group at C-13, the resulting tetracyclic ketone was converted into the methylpiperidine D ring via the in situ *N*-methylation protocol, delivering a known compound **23**, with 48% overall yield in 5 steps, which was used to furnish the (+)-paniculatine, (−)-magellanine, and (+)-magellaninone by Mukai et al.[5g] Although the structure of **23** was not assigned in Mukai's synthesis (our synthetic **23** was elucidated by 2D-NMR; see the SI), treatment of **23** via the Mukaiyama method[18] provided the enone functionality of the A ring, and then hydrolysis of the MOM ether afforded the penultimate compound **24** en route to (−)-magellanine and (+)-magellaninone through one step of Mitsunobu inversion and Dess-Martin oxidation, respectively. In addition, according to Mukai's streamlined protocol (5 steps, one purification), obtaining **23** also means the completion of the formal synthesis of (+)-paniculatine. To our surprise, in our hands, the first step of

dx.doi.org/10.1021/ol502679v | *Org. Lett.* XXXX, XXX, XXX−XXX

L-Selectride reduction of the 13-ketone always gave a 2:1 mixture favoring the α-configured isomer,[19] which could be separated after benzoylation, and then parallel advancing two isomers eventually furnished (+)-paniculatine (**1**) and 13-*epi*-paniculatine (**22**). Our NMR data and optical rotations[20] of synthetic magellanine, magellaninone, and paniculatine are all in agreement with those from literature.

In summary, we present a new strategy for the synthesis of title compounds of tetracyclic diquinane *Lycopodium* alkaloids. Highlights include the rapid and convergent construction of the ABD tricyclic backbone from simple starting materials thioether **7**, allylic iodide **8**, and allyltrimethylsilane. The formidable ABCD tetracycle including complex stereochemistry was constructed through a site-specific and stereoselective aldol cyclization, which was designed by the logic-guided addition of a strategically useful hydroxyl group at C-3 of paniculatine, making the ABD → ABCD tetracyclic formation leading to diquinane *Lycopodium* alkaloids attainable for the first time. The stereochemistry of the compacted framework was scrutinized by X-ray analysis[21] or 2D-NMR. The logic-guided retrosynthetic disconnection producing unconventional strategies[22] could be further applied to other natural products synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, CIF files of compounds **15**, **16**, **18**, and copies of the NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by NSFC (21072200, 21472200) and The Hundred Talents Program of CAS.

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(13) According to the isolated yield of **4**, we conjecture that the undesired isomer of diketone **5** at C-10 could be partially epimerized to the desired one during the basic aldol cyclization.

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(17) The equatorially positioned C-13 hydroxyl or its TBS ether is actually in the top-side of the tetrasubstituted alkene in **17**. That stereochemistry correlation can be more explained by using molecular model or X-ray structures of **16** and **18**.

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(19) To invert the stereochemistry of C-13 from an α- to β-configured alcohol, we have extensively investigated the S_N2 substitution and oxidation−reduction of C-13 ketone on various tetracyclic diquinane substrates. The detailed discussions will be reported in another full paper. We thank Professor Mukai of Kanazawa University and his research assistant for the discussions.

(20) The optical rotations of our synthetic paniculatine, magellanine, and magellaninone are as follows: $[\alpha]_D^{22}$ = +83 (c = 0.18, in $CHCl_3$), $[\alpha]_D^{25}$ = −8.4 (c = 0.18, in $CHCl_3$), and $[\alpha]_D^{24}$ = +73 (c = 0.11, in $CHCl_3$). Mukai et al.[5g] documented the following: $[\alpha]_D^{30}$ = +75 (c = 0.17, in $CHCl_3$), $[\alpha]_D^{30}$ = −20 (c = 0.14, in $CHCl_3$), and $[\alpha]_D^{24}$ = +82.6 (c = 0.16, in $CHCl_3$).

(21) CCDC 1011989 (**15**), 1011990 (**16**), and 1011988 (**18**) contain the supplementary crystallographic data for this paper. These 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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