Total Synthesis of Lycopodium Alkaloids Palhinine A and Palhinine D


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ABSTRACT: The first total syntheses of Lycopodium alkaloids palhinine A, palhinine D, and their C3-epimers have been divergently achieved through the use of a connective transform to access a pivotal hexacyclic isoxazolidine precursor. A microwave-assisted regio- and stereoselective intramolecular nitrone−alkene cycloaddition was tactically orchestrated as a key step to install the crucial 10-oxa-1-azabicyclo[5.2.1]decane moiety embedded in the conformationally rigid isotwistane framework, demonstrating the feasibility of constructing the highly strained medium-sized ring by introduction of an oxygen bridging linker to relieve the transannular strain in the polycyclic scaffold. Subsequent N−O bond cleavage provided the synthetically challenging nine-membered azonane ring system bearing the requisite C3 hydroxyl group. Late-stage transformations featuring a chemo- and stereoselective reduction of the pentacyclic β-diketone secured the availability of our target molecules.

Palhinine-type alkaloids (Figure 1), as members of the Lycopodium family, have a unique 5/6/6/9 tetracyclic or 5/6/6/6/7 pentacyclic ring system characterized with a densely functionalized isotwistane nucleus. Since the isolation of palhinine A from the whole plant of Palhinhaea cernua L. (Lycopodiaceae) by Wang and Long in 2010, isopalhinine A and palhinines B−D have been reported successively by Zhao and Yu in 2013. Although no activity was observed in preliminary studies, scarcity in nature precludes extensive biological evaluations of these alkaloids. Hence, exploration of a general approach for total synthesis of these Lycopodium alkaloids, together with their structurally related analogues, is requisite not only for pursuing the novel molecular architecture but also for investigating their potential bioactivities. To date, four reports on assembly of the functionalized isotwistane (tricyclo[4.3.1.03,7]decane) core have been revealed by She, Maier, Rychnovsky, and our group. Very recently, a sequential protocol involving oxidative dearomatization and tandem hydroxyl oxidation/intramolecular Diels−Alder reaction was elegantly developed by She to install the 6/6/9 tricyclic skeleton of palhinine A. However, total synthesis of palhinine-type alkaloids still remains a challenge in the synthetic community.

Over the past five years, many attempts in our lab have been made to establish the final azonane ring of palhinine A on the functionalized isotwistane framework previously reported. Direct ring construction strategy through either N-substitution (e.g., N-alkylation, Mitsunobu cyclization) (Scheme 1a) or ring-closing metathesis (Scheme 1b) unexpectedly failed to provide the nine-membered azonane ring of palhinine A despite successful implementations in syntheses of related fawcettimine Lycopodium alkaloids.

Considering the inevitably twisted and transannular strain engendered by direct assembly of the azonane ring embedded in the isotwistane framework, an indirect approach involving auxiliary ring construction/deconstruction, which was strategically initiated by a connective transform in the retrosynthetic direction, might be an alternative choice. In view of the generality of connective transform in constructing the medium-size.
Scheme 2. Retrosynthetic Analysis

Scheme 3. Assembly of the Functionalized Isotwistane Building Block

Scheme 4. Construction of Azonane-Containing Auxiliary Ring Embedded in the Isotwistane Scaffold

sized ring, together with the requirement for the site-specific assembly of the requisite oxygenated functional group in the azonane ring, an auxiliary ring system bearing an oxazabicyclo[5.2.1]decane characterized with a unique isoxazolidine moiety in III (Scheme 1) could be conceived by reconnection of the N–O bond in the backbone of palhinine A, wherein introduction of an oxygen bridging linker in the nine-membered azonane ring would be expected to relieve the potential transannular strain. Such an auxiliary ring system might be temporarily installed by an intramolecular [3 + 2] cycloaddition (Scheme 1c) and feasibly provides access to the targeted azonane ring through selective scission of the N–O bond. Interestingly, installation of the isoxazolidine moiety in Lycopodiumicins A and B had led to a putative biosynthetic pathway involving 1,3-dipolar cycloaddition (Scheme 1) could be envisaged from a common synthon for 2 steps. Because of the bulky steric property of the TBS group, formation of the ethylene ketal a priori would be expected to lead to the tautomeric mixture of minor hemiacetal 6a and major hydroxy aldehyde 6b. Subsequent Wittig reaction of 6 gave terminal olefin 7 in 64% yield with the ketone moiety untouched. Then, DMP oxidation yielded aldehyde 8, which was transformed into the inseparable Z/E oxime isomers 9 in 99% yield. The reduction of the oxime group in 9 was achieved with NaBH4CN as the reductive reagent and trifluoroacetic acid as the activator at −40 °C for 30 min, providing hydroxylamine 10 in 90% yield. Notably, higher temperature or longer reaction time partially resulted in reductive cleavage of the ethylene ketal unit in 10.

With functionalized isotwistane 10 in hand, as shown in Scheme 4, two-phase condensation in the presence of 37% aqueous formaldehyde afforded nitroene 11 as a precursor for our designed key nitroene–alkene cycladdition. Because of its instability toward column chromatography, nitroene 11 formed in situ was directly subjected to the optimized microwave conditions (300 W, o-C6H4Cl, 150 °C, 1.5 h) delivering isoxazolidine-containing hexacyclic building block 12 in 52% yield. Its structure and stereochemistry were unambiguously determined by X-ray crystallographic analysis. It should be noted that a simple thermal condition (150 °C) with more than 10 h only gave cycladdition product 12 in ~35% yield. With the possibility of π-facial selective addition of both dipole and dipolarophile components, four presumable transition states (TS-1–TS-4) could be proposed to rationalize the positional and stereochemical aspects of this intramolecular cycladdition. Compared with the unfavorable steric and electrostatic repulsion in TS-2–TS-4, the energetically favorable dipole–dipole attraction as well as the minimal steric interaction in TS-1 might be mostly responsible for the high level of regiocontrol.
Having obtained key common building block 12 with the auxiliary oxa-azabicyclo[5.2.1]decane ring system, as shown in Scheme 5, we then focused our attention on construction of the targeted nine-membered azonane ring in palhinine-type Lycopodium alkaloids. Initial attempts to cleave the isoxazolidine N–O bond in 12 proved to be ineffective by hydrolysis with Pd/C18e or Pearlman’s catalyst18f or reduction with Zn/HOAc.18c For the driving force of its N–O reductive cleavage to be improved, N-methylation was first conducted to give the corresponding quaternary ammonium iodide 13, which was directly exposed to the acidic reductive cleavage condition,18d providing azonane-containing building block 14 in 81% yield. Subsequent removal of the acid-labile protecting group gave 3-epi-palhinine A in 98% yield, and its structure was confirmed by X-ray crystallographic analysis.17 Notably, a distorted twist-chair-boat conformation19 indicated in X-ray structure of 3-epi-palhinine A, a combined sequence for the inversion of C3-OH configuration of C3-OH in palhinine D to be afforded pentacyclic alcohol in 65% yield. After acidic removal of the ketal protecting group, total synthesis of palhinine A was furnished for the first time.

Upon treating 12 with Mo(CO)6 in CH2CN/H2O at elevated temperature,21 a one-pot N–O bond cleavage/hydrolyzation of ethylene ketone/aza-hemiketalization occurred, giving 3-epi-palhinine D in 75% yield. Analogously, its stereochemical utility of 1,3-dipolar cycloaddition in the total synthesis of palhinine-type Lycopodium alkaloids, we describe the first report on total synthesis of palhinine D as well as their C3-epimers. Our route features the development of a combined strategy consisting of microwave-assisted regio- and stereoselective intramolecular nitrene–alkene cycloaddition for the establishment of 10-oxa-1-azabicyclo[5.2.1]decane-containing auxiliary ring and late-stage N–O disconnection for the final release of the key azonane ring. The present synthesis not only chemically demonstrates the utility of 1,3-dipolar cycloaddition in the total synthesis of complex natural products but also tactically illustrates the effectiveness of the auxiliary ring construction/deconstruction approach to assembling the medium-sized ring in some conformationally rigid and sterically congested polycyclic system.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b13401.

Experimental procedures and spectral data (PDF)

X-ray data for compound 12 (CIF), 3-epi-palhinine A (CIF), synthetic palhinine D (CIF), 3-epi-palhinine D (CIF), and compound SI-2-S (CIF)

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**Notes**

The authors declare no competing financial interest.

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■ REFERENCES


(9) As is known, the existence of severe nonbonding interaction in [10] annulene renders its nonplanar structure with nonaromaticity. For such transannular strain to be relieved, a thought-provoking work for the design and synthesis of 1,6-methano[10]annulene through replacing 1,6-internal hydrogen atoms in [10]annulene by a bridging methylene linker was pioneered by Vogel in 1964, giving one classical example of aromaticity driven by the release of transannular strain. For the synthesis of 1,6-methano[10]annulene, see: Vogel, E.; Roth, H. D. Angew. Chem., Int. Ed. Engl. 1964, 3, 228.


(16) For details on the condition optimization of the nitroene–alkene cycloaddition, see the Supporting Information.

(17) The relative configuration was determined by X-ray crystallographic analysis. CCDC 1523463 (12), CCDC 1523464 (3-epi-palinine A), CCDC 1523465 (3-epi-palinine D), and CCDC 1523466 (the synthetic palhinine D) contain the crystallographic data for this paper. The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif.


