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Toward the Total Synthesis of Palhinine A: Expedient Assembly of Multifunctionalized Isotwistane Ring System with Contiguous Quaternary Stereocenters

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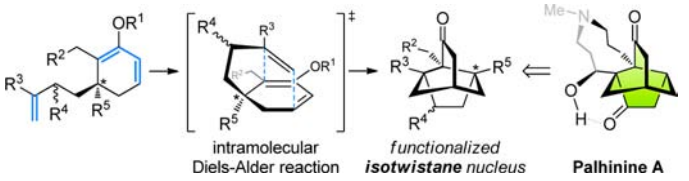
ABSTRACT



The stereoselective, expedient assembly of the key functionalized isotwistane (bridged tricyclo[4.3.1.0^{3,7}]decane) system, 5/6/6 ring, with contiguous quaternary stereocenters in *Lycopodium* alkaloid palhinine A and its analogues via an intramolecular Diels–Alder strategy is described.

The *Lycopodium* alkaloids[1] are unique heterocyclic molecules possessing high structural diversity and significant pharmaceutical potential, and many of them have attracted great interest from biogenetic and synthetic points of view.[2] As a novel $C_{16}N$-type *Lycopodium* alkaloid recently isolated from *Palhinhaea cernua* L. by Long, Wang et al.,[3] palhinine A (Figure 1) with a structure

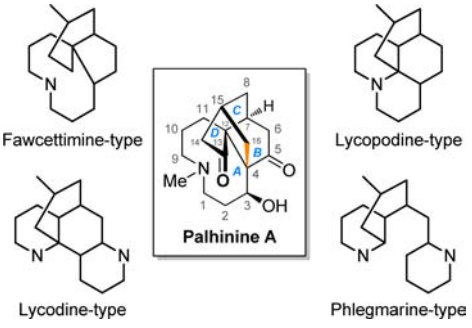


Figure 1. Diverse ring systems in representative major classes of *Lycopodium* alkaloids.

partially related to the fawcettimine-type alkaloids[1e] is featured by a unique 5/6/6/9 tetracyclic ring system containing an unusual bridged carbon–carbon bond between C-4 and C-16, which was elucidated by comprehensive spectroscopic methods and confirmed further by single-crystal X-ray diffraction analysis. Such a fused-bridged

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(1) For some leading reviews, see: (a) Ayer, W. A. *Nat. Prod. Rep.* **1991**, *8*, 455. (b) Ayer, W. A.; Trifonov, L. S. *Lycopodium* Alkaloids. In *The Alkaloids: Chemistry and Pharmacology*; Cordell, G. A., Brossi, A., Eds.; Academic Press: San Diego, CA, 1994; Vol. 45, Chapter 3, pp 233–266. (c) Kobayashi, J.; Morita, H. The *Lycopodium* Alkaloids. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier: San Diego, CA, 2005; Vol. 61, Chapter 1, pp 1–57. (d) Tan, C.-H.; Zhu, D.-Y. *Chin. J. Nat. Med.* **2003**, *1*, 1. (e) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752. (f) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679.

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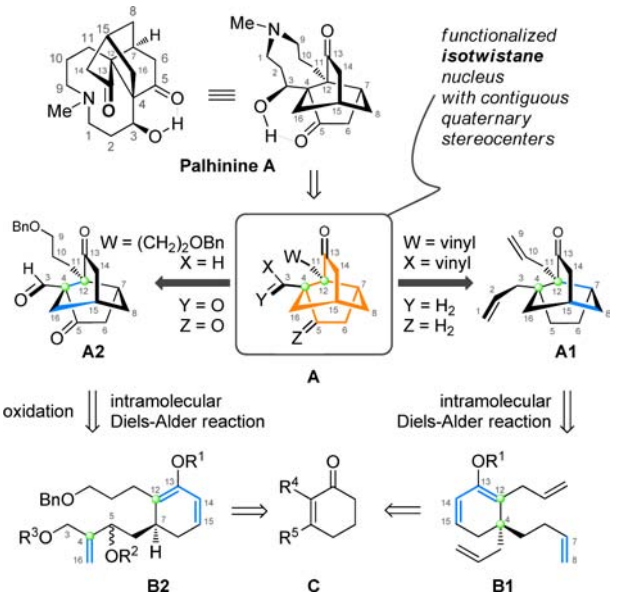
polycyclic structure of palhinine A is architecturally unprecedented in *Lycopodium* alkaloids, and its topological molecular skeleton having five stereogenic centers, two of which (C-4 and C-12) are quaternary, is characterized with a functionalized isotwistane nucleus[4−10] (rings B/C/D, tricyclo[4.3.1.$0^{3,7}$]decane), providing an interesting and challenging target for the synthetic community.

Very recently, an elegant strategy for the stepwise construction of the related isotwistane core has been developed by Xie, She et al.[11] on the basis of tandem oxidative dearomatization/intramolecular Diels−Alder reaction (rings C and D)[12] and the later-stage 5-*exo*-*trig* radical cyclization[4] (ring B). However, the direct assembly of this kind of functionalized isotwistane ring system with contiguous quaternary stereocenters from a monocyclic precursor[8−10] is yet to be explored in the synthetic study of palhinine A. Herein, we report our preliminary efforts toward the expedient and straightforward access to the densely functionalized isotwistane framework by using an intramolecular Diels−Alder strategy.[8,9,13]

Scheme 1. Retrosynthetic Analysis of Palhinine A



Retrosynthetically, the isotwistane **A** (Scheme 1) constitutes the key building block for the synthesis of palhinine A and its analogues. Logically, its nine-membered azonane ring could be conceived by a protocol involving the hydroboration−oxidation and amination from the synthon **A1** or the chemoselective allylation, olefinic oxidative cleavage, and amination from the synthon **A2**. The crucial tricyclic core in **A1** and **A2** could be formally envisioned by intramolecular Diels−Alder cycloaddition of the rationally designed **B1** and **B2**, which could be properly derived from the readily available substituted cyclohexenone **C**. It should be noted that the key stereoselective intramolecular Diels−Alder strategy proposed here would synthetically rationalize the present disconnection, providing an alternative consideration for the straightforward reestablishment of the isotwistane framework of palhinine A as well as its structurally related molecules. The proposed disconnection approach from the bridged tricyclic core **A2** to triene synthon **B2** might be more synthetically interesting due to the elaborated installation of oxygen functional groups requisite for the synthetic study of palhinine A.

Initially to address the feasibility of the efficient construction of functionally simplified tricyclic isotwistane core **A1** from **C** (Scheme 1), we started with known enone **1**[14] (Scheme 2). Disubstituted cyclohexenone **2** was

(4) For selected examples on the construction of the isotwistane core via 5-*exo*-*trig* radical cyclization from the bicyclo[2.2.2]octane system, see: (a) Srikrishna, A.; Reddy, T. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3293. (b) Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2431. (c) Matsushita, T.; Ashida, H.; Kimachi, T.; Takemoto, Y. *Chem. Commun.* **2002**, 814. (d) Singh, V.; Pal, S.; Mobin, S. M. *J. Org. Chem.* **2006**, *71*, 3014 and ref 11.

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(9) For selected examples on the construction of the isotwistane core via an intramolecular Diels−Alder reaction from the cyclohexadienone system, see: (a) Krantz, A.; Lin, C. Y. *J. Am. Chem. Soc.* **1973**, *95*, 5662. (b) Macas, T. S.; Yates, P. *Tetrahedron Lett.* **1983**, *24*, 147. (c) Fráter, G.; Wenger, J. *Helv. Chim. Acta* **1984**, *67*, 1702. (d) Bhamare, N. K.; Granger, T.; Macas, T. S.; Yates, P. *J. Chem. Soc., Chem. Commun.* **1990**, 739. (e) Njardarson, J. T.; McDonald, I. M.; Spiegel, D. A.; Inoue, M.; Wood, J. L. *Org. Lett.* **2001**, *3*, 2435. (f) Spangler, J. E.; Sorensen, E. J. *Tetrahedron* **2009**, *65*, 6739. (g) Mitasev, B.; Porco, J. A., Jr. *Org. Lett.* **2009**, *11*, 2285.

(10) For selected examples on the construction of the isotwistane core via Michael addition/Aldol reaction from the cyclohexenone system, see: Niwa, H.; Wakamatsu, K.; Hida, T.; Niiyama, K.; Kigoshi, H.; Yamada, M.; Nagase, H.; Suzuki, M.; Yamada, K. *J. Am. Chem. Soc.* **1984**, *106*, 4547.

(11) Zhao, C.; Zheng, H.; Jing, P.; Fang, B.; Xie, X.; She, X. *Org. Lett.* **2012**, *14*, 2293.

(12) For selected reviews on the oxidative dearomatization/intramolecular Diels−Alder reaction, see: (a) Liao, C.-C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856. (b) Liao, C.-C. *Pure Appl. Chem.* **2005**, *77*, 1221 and references therein.

(13) For some reviews on the intramolecular Diels−Alder reaction in organic synthesis, see: (a) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41. (b) Brieger, G.; Bennet, J. N. *Chem. Rev.* **1980**, *80*, 63. (c) Ciganek, E. *Org. React.* **1984**, *32*, 1–374. (d) Roush, W. R. Intramolecular Diels-Alder Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 513−550. (e) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (f) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 820. (g) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650. (h) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (i) Takao, K.-i.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* **2005**, *105*, 4779. (j) Tadano, K.-i. *Eur. J. Org. Chem.* **2009**, 4381. (k) Juhl, M.; Tanner, D. *Chem. Soc. Rev.* **2009**, *38*, 2983.

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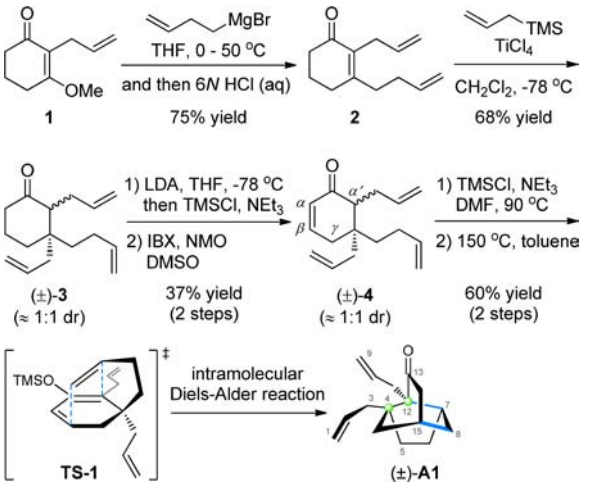
Scheme 2. Synthesis of Tricyclic Synthon (±)-**A1**



accessed in two steps using an alkylation Stork–Danheiser approach.[15] The olefinic ketone (±)-**3** bearing the all-carbon quaternary center was accessed by Sakurai allylation[16] in 68% yield. With (±)-**3** in hand, the regioselective α,β-dehydrogenation of ketone was conducted by using the combined protocol involving the kinetic deprotonation–silylation of (±)-**3** and the subsequent hypervalent iodine-mediated oxidation[17] of the resulting crude silyl enol ether, delivering the desired enone (±)-**4** in 37% yield over two steps. Treatment of enone (±)-**4** with TMSCl in the presence of NEt_3 and DMF at 90 °C resulted in formation of a silyl enol ether. The resulting diene was directly subjected to a thermally promoted (150 °C) intramolecular Diels–Alder reaction. This approach afforded the desired isotwistane core (±)-**A1** in 60% yield over two steps, proceeding through transition state **TS-1** followed by in situ hydrolysis during column chromatography on silica gel. The relative stereochemistry of tricyclic isotwistane (±)-**A1** was unambiguously confirmed by X-ray crystallographic analysis of (±)-**5** (Figure 2),[18] which was obtained in four steps (reduction, silyl protection, hydroboration–oxidation, and iodination) from (±)-**A1**.[19]

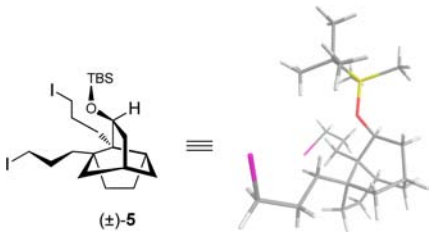
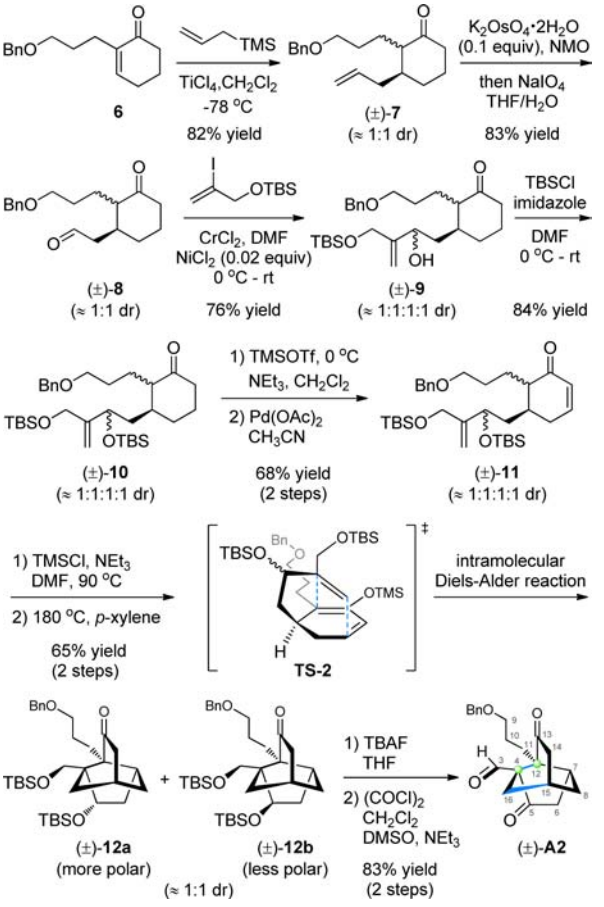


Figure 2. X-ray crystallographic analysis of (±)-**5**.

(15) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

Based on the above-mentioned positive results for the simplified cycloaddition model (**B1**→**A1**, Scheme 1), a synthetic pathway for establishing fully functionalized isotwistane synthon **A2** (Scheme 1) was then explored. The synthesis commenced with Sakurai allylation[16] of readily available enone **6**[20] (Scheme 3), and the disubstituted

Scheme 3. Synthesis of Tricyclic Synthon (±)-**A2**



ketone (±)-**7**[21] was obtained in 82% yield. With (±)-**7** in hand, osmium-catalyzed dihydroxylation followed by $NaIO_4$-mediated oxidative cleavage[22] afforded aldehyde

(16) (a) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673. (b) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200.

(17) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996.

(18) CCDC-883176 for (±)-**5** and CCDC-884247 for (±)-**13** 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.

(19) For details, see the Supporting Information.

(20) For a four-step synthetic protocol to access the enone **6**, see the Supporting Information. Literaturally, the enone **6** was already known: Taber, D. F.; Sheth, R. B. *J. Org. Chem.* **2008**, *73*, 8030.

(21) The chiral **7** could be also accessed by a formal asymmetric conjugate allylation of enones recently reported by Taber et al. This synthetically available chiral synthon will alternatively lead the way for the future study of asymmetric synthesis of palhinine A. Taber, D. F.; Gerstenhaber, D. A.; Berry, J. F. *J. Org. Chem.* **2011**, *76*, 7614.

(22) Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

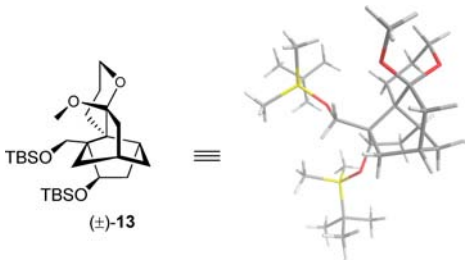


Figure 3. X-ray crystallographic analysis of (±)-**13**.

(±)-**8** in 83% yield. Subsequently, the nickel-catalyzed Nozaki–Hiyama–Kishi reaction[23] was used to chemoselectively couple (±)-**8** and *tert*-butyldimethylsilyl 2-iodoallyl ether (CH_2═C(I)—CH_2O—TBS),[24] affording the desired allylic alcohol (±)-**9** in 76% yield. Following the TBS protection of (±)-**9**, the enone (±)-**11** was formed from (±)-**10** through the kinetic enolization–silylation and Pd-$(OAc)_2$-mediated Saegusa–Ito oxidation.[25] Upon treatment of (±)-**11** with the previously optimized conditions for thermodynamic silyl enol etherification, the resulting silyl ether diene underwent the key intramolecular Diels–Alder cycloaddition via energetically favorable **TS-2** at 180 °C, followed by in situ hydrolysis during column chromatography on silica gel, giving two separable diastereoisomers (±)-**12a** and (±)-**12b** in a combined yield of 65%. The stereochemical assignment of the more polar (±)-**12a** and the less polar (±)-**12b** was further made using X-ray crystallography of (±)-**13** (Figure 3).[18] This was achieved by one-step derivatization of (±)-**12b** (hydrogenolysis followed by in situ ketalization).[19] Finally, the removal of TBS protection of (±)-**12a** and (±)-**12b**, followed by Swern oxidation,[26] accomplished the expedient stereoselective synthesis of (±)-**A2**, which is a synthetically important building block for the study of the total synthesis of palhinine A.

In conclusion, a straightforward synthetic strategy based on the rationally designed intramolecular Diels–Alder reaction has been developed for the efficient assembly of a multifunctionalized isotwistane ring system with contiguous all-carbon quaternary centers in *Lycopodium* alkaloid palhinine A and its deoxy analogue. Of our two approaches, the 10-step synthetic route involving (±)-**A2** will be particularly interesting for the synthesis of palhinine A, due to not only the flexibility of installation of functional groups requisite for its total synthesis but also the feasibility of asymmetric synthesis using the known chiral synthon.[21] Presently, the synthetic study of palhinine A using this strategy is actively under investigation in our laboratory.

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Supporting Information Available. Experimental procedures, characterization data for all new compounds, and X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.