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Studies toward the Synthesis of Palhinine Lycopodium Alkaloids: A Morita–Baylis–Hillman/Intramolecular Diels–Alder Approach

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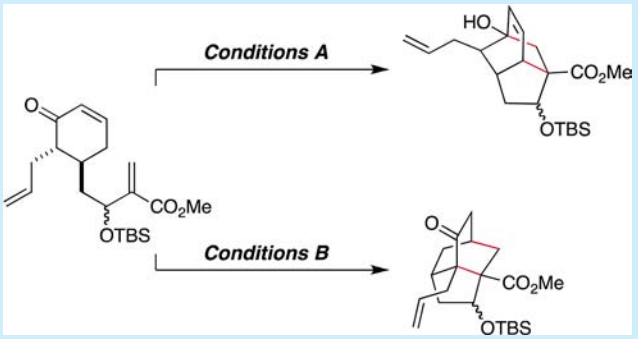
Supporting Information

ABSTRACT: A synthetic route to the isotwistane core of palhinine lycopodium alkaloids is described. A Morita–Baylis–Hillman/intramolecular Diels–Alder (IMDA) strategy sets the vicinal all-carbon quaternary centers present in this family of natural products. The regioselectivity of the IMDA reaction is dictated by the conditions employed for silyl enol ether formation, with one set of conditions providing the core of cardionine and alternate conditions generating the desired isotwistane core of isopalhinine.



Isopalhinine A (**1**) is a lycopodium alkaloid recently isolated from the nodding club moss *Palhinhaea cernua* (Figure 1).[1]

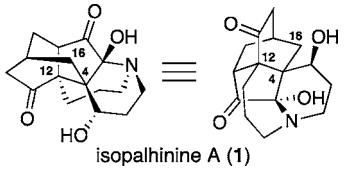


Figure 1. Lycopodium natural product isopalhinine A.

It contains an unprecendented pentacyclic architecture and is the most complex member of the palhinine family of natural products. This family is most closely related to the fawcettimine class of lycopodium alkaloids;[2] however, the palhinine subclass contains a C4–C16 linkage leading to a tricyclo[4.3.1.0^{3,7}]-]decane (isotwistane) core (Figure 2).[3] The unusual architecture of the palhinine family of natural products, including the vicinal quaternary relationship of C4–C12, and the densely functionalized nature of isopalhinine A led us to embark on a total synthesis of **1** utilizing a route that would allow access to the entire family.

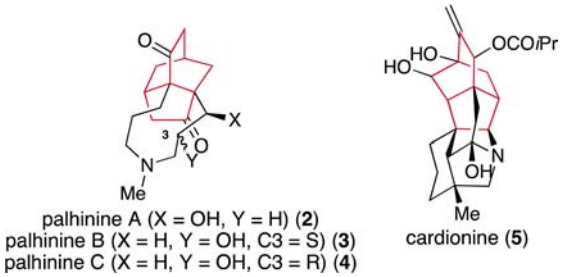


Figure 2. Representative isotwistane containing natural products. The isotwistane core is drawn in red.

The isotwistane motif is found in a variety of natural products including palhinine and cardionine (Figure 2).[4] Several groups have developed methods for isotwistane construction.[5] In addition, there have been three reported approaches to palhinine A.[6] The first report by She and co-workers utilizes an oxidative dearomatization/intramolecular Diels–Alder (IMDA) sequence for construction of the [2.2.2] bicycle, which was subsequently elaborated to a functionalized isotwistane. Gaugele and Maier described an approach to the isotwistane core employing a domino Michael, Arndt–Eistert homologation, intramolecular aldol sequence. Most pertinent to this discussion is the Nozaki–Hiyama–Kishi/IMDA strategy developed by Fan and co-workers, which demonstrated the feasibility of setting the vicinal quaternary center through an IMDA reaction.

A retrosynthetic analysis is shown in Scheme 1. We rationalized that a late-stage installation of the azanone ring using Fukuyama's nosyl cyclization strategy[7] and further functionalization to the natural products could lead back to differentially functionalized isotwistane **6**. Isotwistane **6** was envisioned as arising from an intramolecular Diels–Alder reaction that simultaneously sets the required vicinal quaternary centers. This strategy offered synthetic flexibility to access the entire family by providing three oxygen-bearing carbons at distinct oxidation states. A Morita–Baylis–Hillman reaction[8] could be used to install the dieneophile fragment of siloxydiene **7**. Standard enolate manipulations would lead back to aldehyde **8**, which should be accessible from cyclohexenone.

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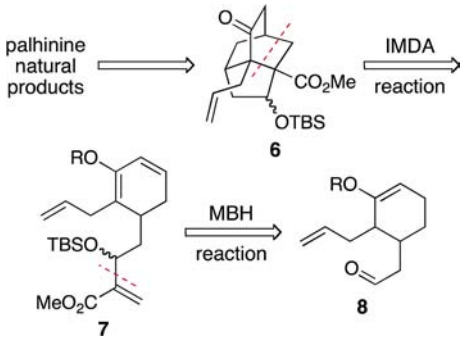
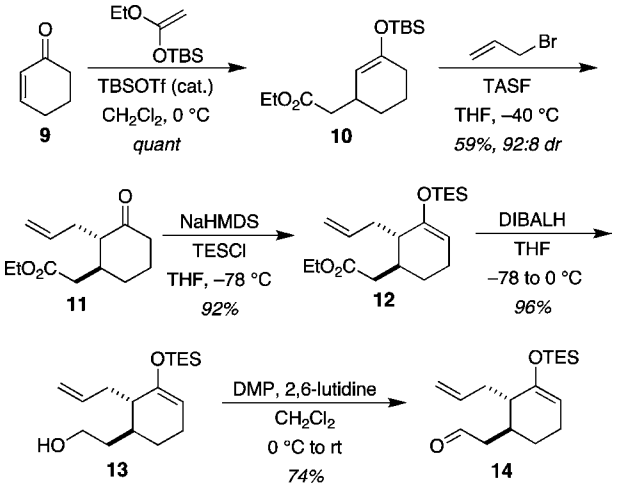
Scheme 1. Retrosynthetic Analysis of Palhinine Natural Products



Initial studies toward the synthesis of aldehyde **8** included Jørgensen's organocatalytic enone synthesis[9] and malonate Michael sequences, but neither proved convenient. Inspired by Wilson and Trauner's synthesis of (+)-SCH 642305,[10] we turned our attention to a Mukaiyama–Michael approach to the Diels–Alder precursor. It should be noted that an enantioselective varient of this reaction utilizing cyclohexenone has been reported.[11]

Our Mukaiyama–Michael strategy to aldehyde **14** is outlined in Scheme 2. Treatment of cyclohexenone with the silyl ketene

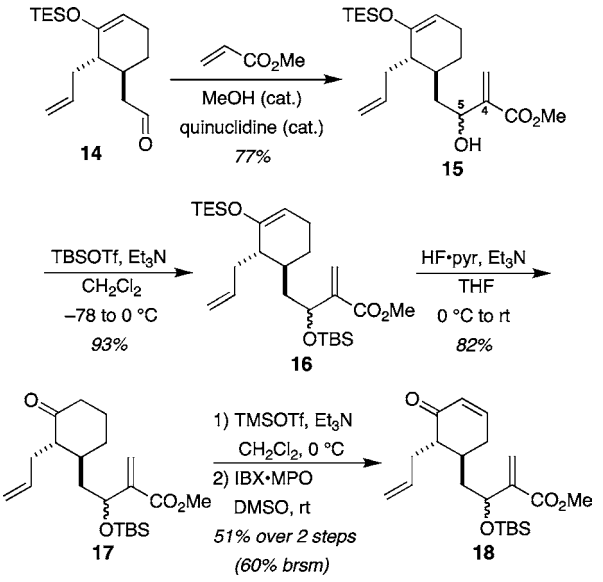
Scheme 2. Mukaiyama–Michael Approach to the Morita–Baylis–Hillman Precursor



acetal of ethyl acetate in the presence TBSOTf resulted in conjugate addition and silyl transfer to afford silyl enol ether **10** in high yield. One advantage of this approach is that the regioselective generation of silyl enol ether **10** provides a natural point of introduction for the required allyl side chain. This transformation was achieved by the use of allyl bromide and tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[12] to afford ketone **11**.[13] This tandem vicinal difunctionalization[14] simplifies the synthetic sequence to aldehyde **14** by differentiating the α and α' positions of ketone **11**. Kinetic deprotonation of ketone **11** under hard enolization conditions and trapping as TES enol ether **12** served two roles: first, to mask the ketone functionality and, second, to serve as the handle for oxidation to the enone. Ester **12** was converted to alcohol **13** by reduction with DIBAL-H, which was subsequently oxidized to aldehyde **14** by treatment with Dess–Martin periodinane[15] in the presence of 2,6-lutidine.

With functionalized aldehyde **14** in hand, methods to forge the C4–C5 bond and elaborate the cyclohexyl ring were investigated (Scheme 3). Treatment of aldehyde **14** with

Scheme 3. Synthesis of Key Enone for Intramolecular Diels–Alder Reaction



methyl acrylate in the presence of catalytic amounts of methanol and quinuclidine provided excellent yields of allylic alcohol **15** as an inconsequential 1:1 mixture of diastereomers.[16] Allylic alcohol **15** was protected as TBS ether **16** to prevent mixed ketal formation upon hydrolysis of the enol ether moiety. Unfortunately, attempts at direct oxidation of TES enol ether **16** proved challenging primarily due to low reactivity. Both the Tsuji modification of Saegusa–Ito oxidation,[17] and Nicolaou's IBX·MPO protocol[18] primarily led to mixtures containing mostly recovered starting material with traces of ketone **17**, suggesting that insertion into the O–Si bond is not efficient and the resultant enolate is more easily protonated than oxidized. To circumvent this issue, TES enol ether **16** was selectively hydrolyzed upon treatment with HF·pyridine to afford ketone **17**. Soft enolization of ketone **17** using TMSOTf and triethylamine afforded the TMS enol ether, which could be directly oxidized to desired enone **18** in moderate yields using IBX·MPO.

Initial attempts to perform the intramolecular Diels–Alder reaction of enone **18** using the soft enolization conditions (conditions A: TMSOTf, Et_3N) followed by heating in *o*-dichlorobenzene (DCB) led to a mixture of regioisomers (Scheme 4). In this case, the major products were the isotwistanes arising from γ-deprotonation of enone (linear-conjugated siloxydiene **19**), as opposed to α-deprotonation (cross-conjugated siloxydiene **20**). The product distribution is believed to be the result of modest regioselectivity of siloxydiene formation, based on NMR spectroscopic analysis, rather than a reversible 1,5-hydride shift occurring during the IMDA reaction.

The major product of this IMDA reaction was isotwistane **21**. It is not useful for the synthesis of palhinine lycopodiums, but it contains the core of delphinium alkaloid cardionine **5**.[4a] Interestingly, the mismatched electronic activation of the diene and dienophile did not derail the cyclization; decalin products

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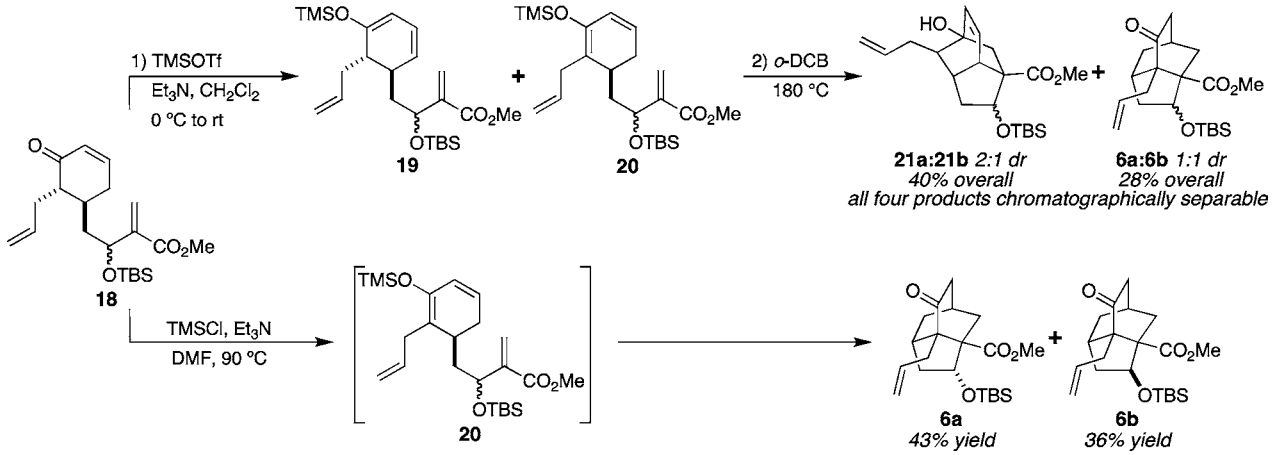
Scheme 4. Regioselectivity in the Intramolecular Diels–Alder Reaction



resulting from Michael addition of the silyl enol ether moiety into the acrylate fragment were not observed.

Using conditions previously described for cross-conjugated siloxydiene formation,[6b] selective formation of the desired Diels–Alder precursor was anticipated. These conditions unexpectedly led to the IMDA products directly. Thus, upon heating enone **18** to 90 °C in DMF in the presence of excess TMSCl and Et_3N (conditions B), the sole isolated products were diastereomeric isotwistanes **6a** and **6b** in high yield. This surprising result suggests that despite mismatched electronics and a demanding steric environment, this IMDA reaction is particularly facile. Computational studies to better understand the energetics of both cyclizations are currently underway.

In summary, a synthetic route to differentially functionalized isotwistanes **6a** and **6b** has been developed (10-steps, 12% overall yield from cyclohexenone). The key features of this approach are the use of a Mukaiyama–Michael/allylation sequence to rapidly access key aldehyde **14**, which efficiently undergoes a Morita–Baylis–Hillman reaction to install the dienophile fragment. The regiochemical outcome of the IMDA reaction depends on the conditions employed for silyl enol ether formation. Desired isotwistanes **6a** and **6b** were accessed under surprisingly mild conditions.

This validated strategy sets the stage for a synthetic approach to isopalhinine and other alkaloids in its class. Alternate enolization conditions lead to the cardionine isotwistane core, providing an interesting starting point for its synthesis. Applications of these strategies to the natural products in racemic and asymmetric forms is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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