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Synthetic studies towards (±)-isopalhinine A: Preparation of the bicyclic core *via* Nazarov cyclization

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ABSTRACT

This manuscript describes progress towards the total synthesis of (±)-isopalhinine A wherein an allene ether Nazarov cyclization gives rise to the bicyclic core.

Isopalhinine A (**1**) was isolated in 2013 by Zhao and co-workers and represents a new and interesting lycopodium alkaloid natural product [1]. Specifically, isopalhinine A (**1**) belongs to the fawcettimine subclass and is distinguished by the presence of an N-C5 bond and the corresponding 1-azabicyclo [4.3.1] decane moiety (Fig. 1). Many natural products in this family possess interesting biological activities, however similar properties for isopalhinine A have yet to be delineated [1].

Despite the apparent lack of biological activity, isopalhinine A (**1**) was seen as an intriguing target given its 5/6/6/6/7 fused ring system which bears a cycloheptane hemiaminal and four contiguous stereocenters, two of which are adjacent quaternary centers [2]. The structure also contains an imbedded isotwistane moiety (highlighted in blue).

As illustrated retrosynthetically in Scheme 1, we envisioned isopalhinine A (**1**) as arising *via* a series of ring closing events that would be initiated from bicyclic enone **2**. In turn, enone **2** was expected to derive from an allene intermediate (**3**) *via* Nazarov cyclization. Setting the stage for the Nazarov would involve coupling Weinreb amide **4** with a metalated variant of allene **5**. The latter two intermediates were seen as deriving from 1,3-diketone **6** and propargyl alcohol (**7**), respectively.

In a forward sense, our efforts began by accessing allene **5**, one of the key components of the allenic Nazarov cyclization. To this end, commercially available propargyl alcohol **7** was advanced to the corresponding MOM ether (**8**) which, upon exposure to potassium *tert*-butoxide, underwent isomerization to allene **9** (Scheme 2) [3]. Subjecting **9** to α-lithiation and quenching with trimethyl silyl chloride (TMSCl) furnished TMS protected allene **10** [4]. Interestingly, γ-lithiation of **10** followed by addition of a THF solution of tosyl aziridine (**11**) [5] produced the corresponding bis-TMS protected allene **12** in modest yield. The unexpected formation of **12** clearly indicated intermolecular silyl scrambling and led to a brief investigation of this event which involved subjecting **10** to the same metalation conditions followed by quenching with a proton source. These latter conditions cleanly and efficiently returned starting material, thus indicating the initially formed allenic anion is stable under the reaction conditions and scrambling of the TMS groups likely occurs subsequent to homologation with tosyl aziridine **12**. This observation suggests that the sulfonyl amide anion, formed upon aziridine opening, may play a critical role in this TMS scrambling event.

At this stage, rather than optimizing the preparation of the allene intermediate, we opted to push forward (Scheme 3). Thus, **12** was treated with benzyl chloroformate (**13**) to furnish the corresponding benzyl urethane (**14**) which, upon exposure to magnesium, undergoes cleavage of the sulfonamide to provide allene **15** [6]. Exposure of **15** to tetrabutylammonium fluoride (TBAF) delivers the desired allene (**5**) in good yield.

With the desired allene in hand, we turned our attention to the preparation of the Weinreb amide intermediate (**4**). Toward this end, exposure of known 1,3-diketone **6** [7] to sodium hydride fol-

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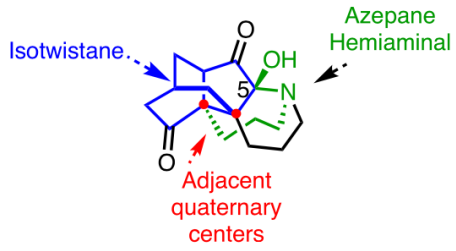
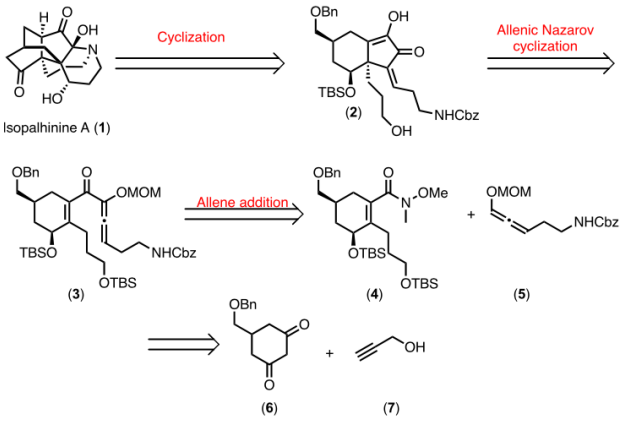
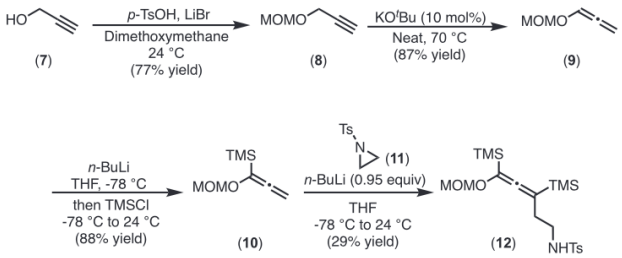


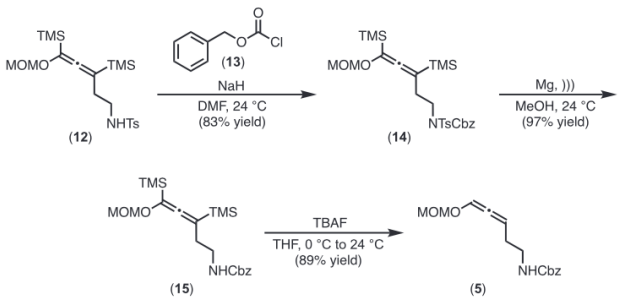
Figure 1. Isopalhinine A (**1**).



Scheme 1. Retrosynthetic analysis of isopalhinine A.

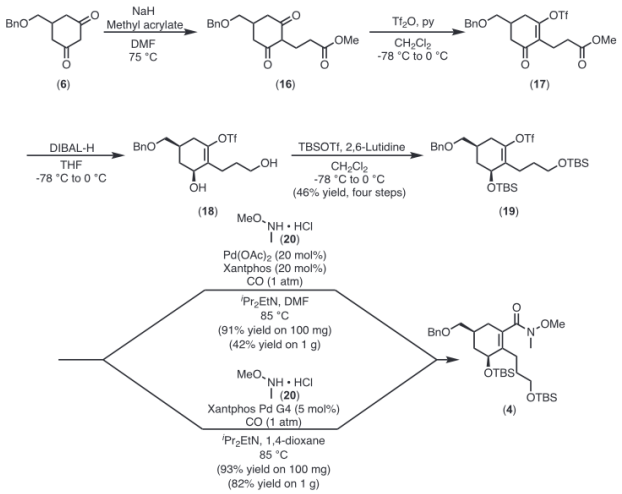


Scheme 2. Synthesis of bis-TMS allene.



Scheme 3. Formation of the desired allene.

delivered Michael adduct **16** (Scheme 4). Next, **16** was converted to the corresponding enol triflate **17** which, when exposed to DIBAL-H undergoes global reduction to give diol **18** as a single diastere-

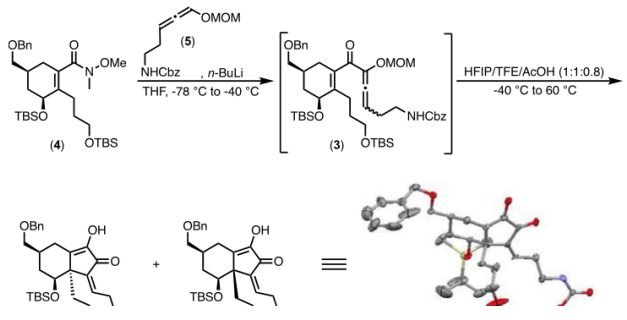


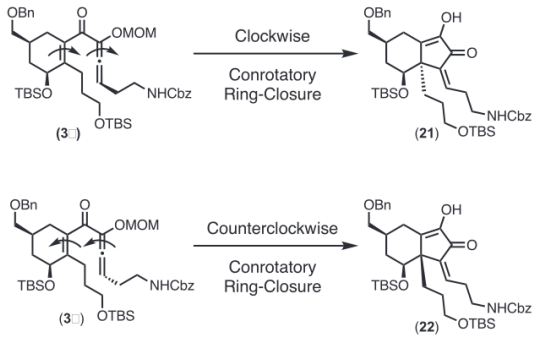
Scheme 4. Synthesis of Weinreb amide precursor.

N,O-dimethylhydroxylamine hydrochloride (**20**) under an atmosphere of CO in DMF efficiently produces **4** (91% yield) when the reaction scale is maintained below 100 mg [9]. However, efforts to apply these conditions to gram scale reactions were met with a significant loss in efficiency (42% yield). Fortunately, we eventually discovered that changing to the Xantphos Pd G4 precatalyst developed by Buchwald, coupled with 1,4-dioxane as the solvent, was quite efficient on both multimilligram and gram scale reactions [10].

Having accessed the two key components (**4** and **5**) we turned toward the key allene ether Nazarov cyclization. In the event, exposure of allene **5** to *n*-BuLi followed by addition of Weinreb amide **4** was expected to produce intermediate **3** which, upon exposure to acid would undergo the allene ether Nazarov cyclization (Scheme 5). Initial studies employing conditions pioneered by Tius (1 M NaH_2PO_4 or silica gel) failed to give any of the desired electrocyclization products [11]. Taking further inspiration from previous studies by Tius, wherein exposure of divinyl ketones to strong acid in the presence of trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) induces electrocyclization, we explored other acids [12]. In initial studies employing HCl the desired product was indeed observed, albeit in low yield. However, when intermediate **3** was allowed to react in a solution containing a weaker acid, AcOH, (HFIP/TFE/AcOH@1:1:0.8) at 60 °C the desired allene ether Nazarov cyclization proceeded to produce the bicyclic products

y





Scheme 6. Stereochemical outcome of Nazarov cyclization.

21 and **22** in 67% yield as a separable mixture of diastereomers (1:1). Fortunately, the latter compound is a crystaline solid and proved amenable to structural confirmation by single crystal X-ray analysis [13].

In rationalizing the stereochemical outcome of the reaction, it is perhaps easiest to first focus on the observed formation of only the Z-alkene isomers. As detailed in a study by Boyd and Brunell, this result is governed by torquoselectivity [14]. The latter dictates that the conrotatory ring closure proceeds so as to minimize the interaction of substituents at the termini of the alkene and allene. Given that the alkene is tetrasubstituted the sense of torquoselectivity is governed by the stereogenicity of the allene moiety. Thus, as illustrated in Scheme 6 the 1:1 mixture of the diastereomeric Nazarov products derives from the initially formed diastereomeric mixture of allene adducts (3α and 3β) which, undergo torquoselective conrotatory ring closures in clockwise and counterclockwise directions (viewed from the termini undergoing bond formation).

In ongoing efforts toward a synthesis of isopalhinine A, we have accessed cyclopentanones **21** and **22** through the use of an allenic Nazarov cyclization in eight linear steps from known starting materials in a convergent fashion. Having installed all of the requisite carbon atoms, current efforts are focusing on completing the total synthesis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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3