Organic LETTERS

Letter

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An Iminium Ion Cascade Annulation Strategy for the Synthesis of Akuammiline Alkaloid Pentacyclic Core Structures

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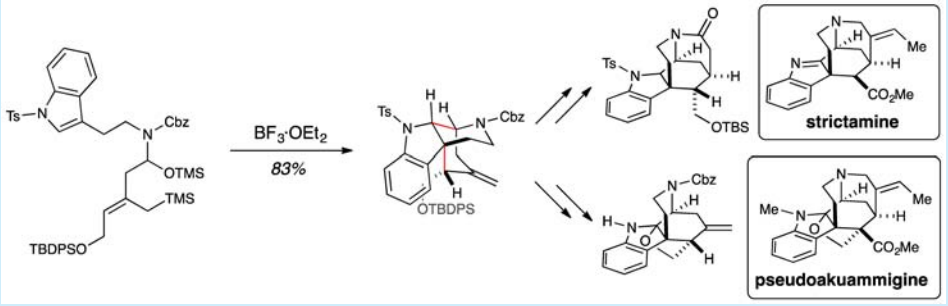
Supporting Information



ABSTRACT: The akuammiline alkaloids are a family of indole monoterpene natural products known for their polycyclic cage-like structures. An iminium ion cascade annulation approach was developed, simultaneously synthesizing both the C and D rings of these natural products by annulation onto a protected indole ring. This reaction allowed the synthesis of a key tetracyclic intermediate toward these natural products. This tetracycle was used for the synthesis of the pentacyclic methanoquinolizidine core present in such alkaloids as akuammiline and strictamine as well as the pentacyclic furoindoline core found in pseudoakuammigine.

The akuammiline alkaloids are a family of natural products that have been known for well over a century. These indole monoterpenoids display promising biological activity, such as anticancer, anti-inflammatory, and antimalarial activities.[1] Additionally, they are known for their cage-like polycyclic structures, arising from their characteristic C7−C16 bond. For decades, their complex structure has presented a significant challenge to synthetic chemists;[2] only relatively recently have total syntheses of any of these natural products been completed.[3] One particular subclass of these alkaloids, those that contain a methanoquinolizidine core (Figure 1A, **1**−**3**), has been particularly challenging to access, with successful total syntheses only being completed within the past year.[4]

Our approach to these natural products centers on a strategy differing from that used in prior successful syntheses. Previous total syntheses by Garg and Zhu both centered on stepwise annulation around a preformed C ring core.[4a,b] In an alternative approach, we viewed a retrosynthetic disconnection within this central C ring as being a significantly simplifying transform. This strategy leads to a complementary disconnection in which a strategic cascade annulation would simultaneously form the C and D rings, each appropriately decorated to append the E ring (Figure 1B). We hypothesized that we could employ this strategy in the synthesis of tetracyclic intermediate **3** from hemiaminal **4** via an iminium ion cascade annulation. This cascade would begin with reaction of an iminium ion, formed by Lewis acid mediated decomposition of hemiaminal **4**, on the 2-position of the indole. Before rearomatization could occur, the subsequently formed benzylic carbocation would be

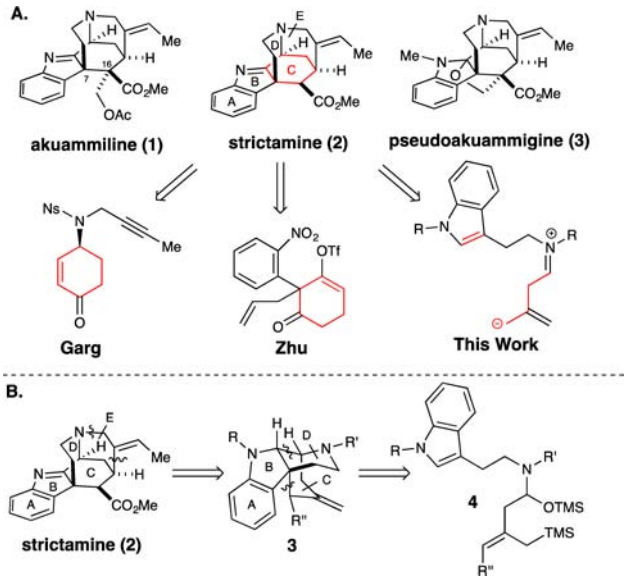


Figure 1. (A) Representative akuammiline alkaloids and key retrosynthetic intermediates in the synthesis of strictamine. (B) Retrosynthetic analysis from strictamine.

Received: November 15, 2016
Published: December 1, 2016

DOI: 10.1021/acs.orglett.6b03406
Org. Lett. 2016, 18, 6492−6495

trapped by an appropriately positioned nucleophile, forging the key C7−C16 bond.

Previously, our laboratory has developed cascade reactions for the synthesis of stereochemically unusual indole alkaloids. During these investigations, we established that cascade annulations from related iminium ion precursors[6] could be controlled to regioselectively produce the core of the Malagasy alkaloids or the core of the akuammiline alkaloids (Figure 2).[7]

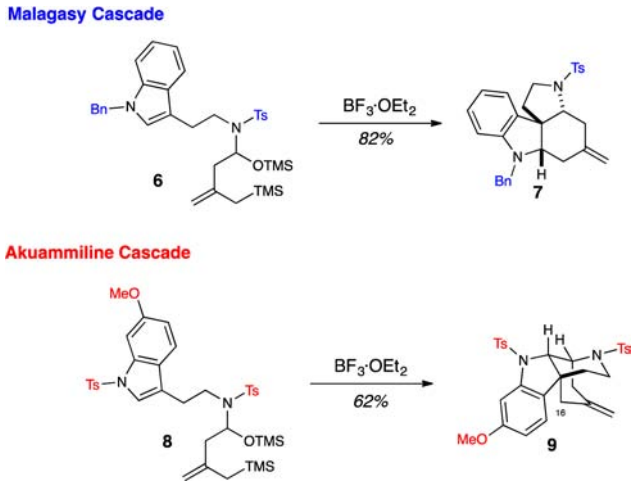


Figure 2. Preliminary investigations of regiodivergent reactions for the Malagasy and akuammiline alkaloids.

Use of an electron-donating group (Bn) on the indole nitrogen in hemiaminal ether **6** promoted the C3 attack of the subsequently formed iminium ion, leading to the Malagasy alkaloid core **7** in 82% yield. An indole substitution pattern that promoted C2 nucleophilicity (6-methoxy) and suppressed C3 nucleophilicity (*N*-Ts) in hemiaminal ether **8** resulted in regiodivergent tetracycle **9** in 62% yield, resembling the core of the akuammiline alkaloids.

While this result demonstrated that such a regiodivergent cascade was possible, there were some readily apparent challenges in using this specific core in the synthesis of these natural products. This product was initially observed with a substrate containing a 6-methoxy substituent on the indole, but none of the akuammiline alkaloid targets are oxidized in this position. Additionally, the use of tosyl protecting groups on both the indole and hemiaminal nitrogens does not provide synthetically useful differentiation of these amines. Finally, this tetracyclic intermediate contains no substitution at C16, a key feature in these natural products that would be difficult to introduce later in any synthetic route. Therefore, an alternative cascade substrate would be necessary in order to provide a tetracyclic core of greater synthetic utility.

Our initial studies explored whether a regiodivergent cascade would be possible without the reinforcement of a 6-methoxy substituent on the indole (Figure 3A). During the development of cascade reactions toward the synthesis of the Malagasy alkaloids, we had observed that protection of the hemiaminal ether nitrogen as a carbamate (Cbz) typically provided a Pictet−Spengler product, the result of C2 attack of the intermediate iminium ion.[6] We hypothesized that combining this protection pattern with *N*-tosyl substitution on the indole could potentially provide the regiodivergent product we desired. Indeed, decomposition of hemiaminal ether **10**[8] under Lewis acidic conditions provided tetracycle **11a**[9] in

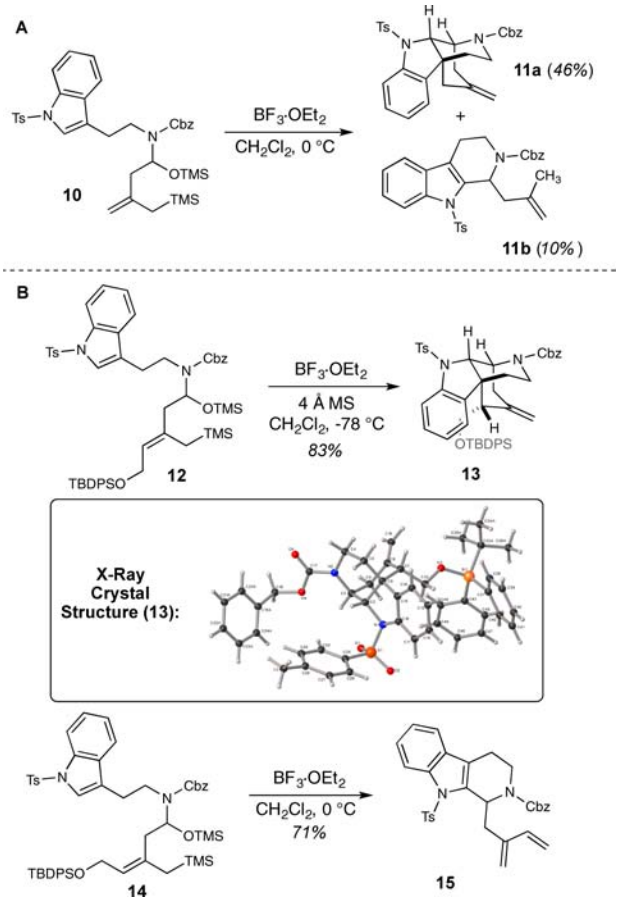


Figure 3. (A) Development of cascade annulation with new protection pattern. (B) Cascade annulations with trisubstituted allylsilanes.

46% yield along with 10% of protodesilylated Pictet−Spengler cyclization product **11b**.

Upon finding a suitable nitrogen substitution pattern that could provide our desired topology without unnecessary substituents on the indole ring, we next explored the effect of utilizing trisubstituted allylsilanes (Figure 3B) to provide the C16 substitution necessary for a synthetically useful tetracyclic core. Our previously developed Malagasy cascade was found to be tolerant of more substituted allylsilanes, transferring olefin geometry into C16 diastereocontrol with high levels of selectivity, subsequently providing access to the natural product malagashanine.[7] However, the allylsilane moiety would add to a tertiary carbocation in the akuammiline cascade, making it unclear whether this addition could successfully occur. We found that tolerance of trisubstituted allylsilanes in the cascade was dependent upon olefin geometry. Hemiaminal ether **12**[8] with *Z*-allylsilane geometry successfully cyclized under Lewis acidic conditions to provide the substituted tetracycle **13**[9] as a single diastereomer in 83% yield, with the relative stereochemistry confirmed by X-ray crystallography. This provided us with a tetracyclic core containing a synthetically useful substitution pattern. However, hemiaminal ether **14**[8] with *E*-allylsilane geometry provided Pictet−Spengler product **15** in 71% yield, the result of rearomatization and allylsilane decomposition under the Lewis acidic conditions.

This observed product selectivity was rationalized by analysis of the possible transition states for the allylsilane addition step (Figure 4). Examination of the chair-like transition states for both substrates **12** and **14** reveals significant transannular strain

DOI: 10.1021/acs.orglett.6b03406
Org. Lett. 2016, 18, 6492−6495

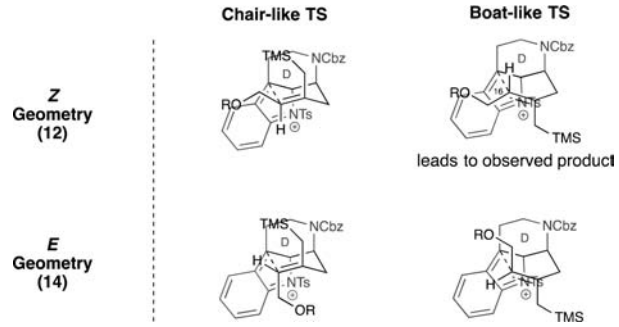


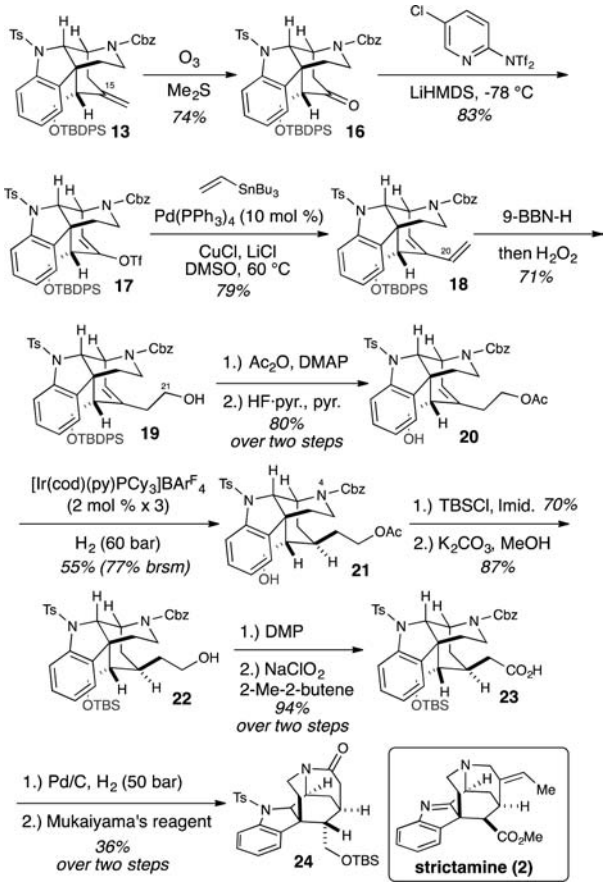
Figure 4. Rationale for selectivity in cyclization of hemiaminal ethers **12** and **14**.

between the allylsilane and the already formed D ring. Instead, the observed stereochemistry in tetracycle **13** corresponds with that expected from a boat-like transition state for allylsilane addition. Invoking a similar transition state for substrate **14** instead reveals significant additional eclipsing interactions between the allylsilane and the already formed D ring. Therefore, *E* allylsilane isomer **14** faces significant steric hindrance in either possible transition state for allylsilane addition, leading to competitive rearomatization that provides Pictet–Spengler product **15**. The stereochemistry at C16 may potentially be epimerized in later steps of a synthetic route, providing incentive to move tetracycle **13** forward in subsequent studies.

With tetracyclic intermediate **13** in hand, we next focused our efforts on the synthesis of the pentacyclic core present in akuammiline (**1**) and strictamine (**2**) (Scheme 1) via annulation of the final E ring. Our strategy centered on using the C15-containing olefin as a functional handle to annulate the rest of the E ring as well as set the crucial stereochemistry of the bridgehead position. Ozonolysis of the exocyclic olefin in tetracycle **13** readily provided ketone **16** in 74% yield, revealing a new functional handle for coupling the required two carbon fragment onto C15 that was necessary to build the final ring. Ketone **16** was converted to vinyl triflate **17** in 83% yield via formation of the kinetic enolate with LiHMDS followed by trapping with Comin's reagent[10] at −78 °C. Stille reaction of vinyl triflate **17** with (vinyl)tributylstannane subsequently forged the key C15–C20 bond, providing diene **18** in 79% yield.[11] Selective hydroboration of the terminal portion of the diene with 9-BBN-H followed by oxidation provided homoallylic alcohol **19** in 71% yield, providing a C21 functional handle that could be used later for ring closure.

Our next goal was the diastereoselective reduction of the internal olefin in the C ring, setting the stereochemistry of the important C15 bridgehead carbon. While synthesis of our desired diastereomer would involve hydrogenation of the more accessible face of the olefin, there were still significant steric challenges due to such a hydrogenation occurring on the concave face of the fused B/C ring system. We hypothesized that the free alcohol functionality sitting axially on the C16 stereocenter could direct hydrogenation to the desired face via coordination with an appropriate homogeneous catalyst. Synthesis of the appropriate substrate required acetylation of the C21 primary alcohol, followed by cleavage of the TBDPS ether with HF·pyridine, providing homoallylic alcohol **20** in 80% yield over two steps. Initial attempts at directed homogeneous reduction of trisubstituted olefin **20** with Crabtree's catalyst $[Ir(cod)(py)(PCy_3)]PF_6$ proved unsuccessful over a wide range of pressures and catalyst loadings (see Supporting Information for details).[12] Using 2 mol % of the $BAr^F{}_4^-$ analog[13] of Crabtree's catalyst at 60 bar hydrogen pressure provided the desired reduction product **21** in 26% yield, but increased pressure and catalyst loading appeared to inhibit reactivity. Crabtree's catalyst and its analogs are known to undergo deactivating trimerization under hydrogenation conditions if reactivity with olefin is slow.[12a] In order to remedy this, we found that dosing an additional 2 mol % of the catalyst twice at 36 and 72 h provided the desired reduction product **21** in 55% yield along with 23% recovered starting material, with the desired C15 stereochemistry confirmed by observation of several key NOE correlations in the NOESY spectrum of this compound.[9]

Scheme 1. Synthesis of Pentacycle 24



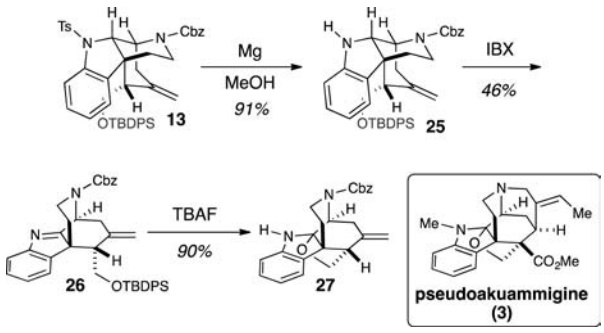
With the appropriate C15 stereochemistry now set, we next sought out closure of the final E ring via lactamization between a C21 carboxylic acid and a free N4 nitrogen. The directing alcohol **21** was protected as the TBS ether in 70% yield followed by subsequent acetate removal to furnish C21 alcohol **22** in 87% yield. Oxidation with Dess-Martin periodinane[14] followed by Pinnick–Lundgren oxidation[15] provided carboxylic acid **23** in 94% yield over two steps. Cbz protecting group removal using 10% Pd/C under 50 bar of hydrogen gas, followed by reaction of the resultant amino acid with Mukaiyama's reagent,[16] provided the cyclized pentacyclic core **24** in 36% yield over two steps, with this structure confirmed by observation of key HMBC correlations.[9]

The tetracyclic intermediate **13** was further used to investigate the formation of the pentacyclic furoindoline core present in such akuammiline alkaloids as pseudoakuammigine

DOI: 10.1021/acs.orglett.6b03406
Org. Lett. 2016, 18, 6492–6495

(3) (Scheme 2). The tosyl group on the indoline nitrogen was removed using magnesium powder in MeOH under sonication

Scheme 2. Synthesis of Pentacycle 27



to provide free amine **25** in 91% yield. Subsequent oxidation with IBX provided indolenine **26**[9] in 46% yield. Cleavage of the TBDPS ether with TBAF followed by spontaneous cyclization provided pentacyclic core **27** in 90% yield. This structure was confirmed by observation of a key HMBC correlation between the $-CH_2-$ of the furoindoline ring and the hemiaminal ether carbon.[9]

In conclusion, we have developed a cascade annulation reaction that provides access to a highly substituted tetracyclic intermediate for the akuammiline alkaloids. This intermediate can be converted into the challenging methanoquinolizidine core intermediate present in the alkaloids strictamine and akuammiline, as well as the furoindoline core present in pseudoakuammigine. However, the conversion of tetracycle **13** to pentacyclic strictamine core **24** remains inefficient, and the utilized cyclization strategy delivers racemic products. Current studies in our laboratory are exploring strategies for the synthesis of these natural products that address these issues, the results of which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03406.

Experimental pocedures and NMR data (PDF)
X-ray crystallography data for **13** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the NSF (CHE-1362502). NMR studies for this research were performed on instrumentation funded by the NSF (CHE-1531620). We gratefully acknowledge Ricardo Delgado (Department of Chemistry, Emory University) for conducting preliminary experiments and Dr. John Bacsa (Emory X-ray Center) for assistance with X-ray structural analysis.

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(8) For details about the synthesis of hemiaminal ethers **10**, **12**, and **14**, please see the Supporting Information.

(9) For details about the structural assignment of **11**, **13**, **21**, **24**, **26**, and **27**, please see the Supporting Information.

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Org. Lett. 2016, 18, 6492−6495