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Observations arising from a Beckmann rearrangement-Mannich cyclization approach to the azepinobisindole alkaloid iheyamine A

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ABSTRACT

An overview of an iterative Beckmann rearrangement-Mannich cyclization approach to the azepinobisindole alkaloid iheyamine A is described. In a preliminary model study, the (*E*)-oxime **10** underwent Beckmann rearrangement to give the bisindolylacetamide **4** followed by an intramolecular Mannich cyclization affording 2-(indolin-2-yl)indole **5** containing the heterocyclic framework of the iheyamine alkaloids. However, the 2-(indolin-2-yl)indole **5** could not be converted into the azepinobisindole core of iheyamine A. When the same Beckmann-Mannich approach was applied toward the natural product itself, a result was obtained that contrasted the model study. The (*E*)-oxime **3** did not undergo Beckmann rearrangement, but instead an intramolecular Mannich cyclization whereby the electron rich C4 site attacked the intermediate iminum ion, generating the 4-(indolin-2-yl)indole **25** bearing the heterocyclic framework of the slime mould pigment arcyriacyanin A. Although this route did not result in the synthesis of iheyamine A being accomplished, some interesting observations related to the venerable Beckmann rearrangement and Mannich cyclization reactions are described.

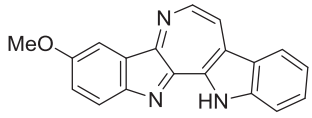
1. Introduction

Iheyamines A (**1**) and B (**2**) were isolated from the ascidian *Polycitorella* sp. collected off Iheya island, Okinawa (Fig. 1).[1] The unique azepinobisindole scaffold present in these alkaloids inspired our research group to recently complete a total synthesis of iheyamine A using a route featuring a cross-Mannich reaction to forge the 2,2′-bisindole bond.[2] Prior to this successful synthesis, a distinct synthetic route to iheyamine A was pursued, the details of which are reported herein.

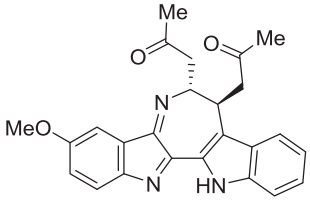
Our initial plan was to develop a procedure to simultaneously integrate nitrogen into the indole 3-position and build the azepine heterocycle in a one-pot operation (Scheme 1). Along these lines, it was predicted that under acidic conditions, (*E*)-oxime **3** would undergo a stereospecific Beckmann rearrangement[3] to form bisindolylacetamide **4** followed by an intramolecular Mannich cyclization[4,5] to give the 2-(indolin-2-yl)indole **5**. Given that **5** contained the complete skeleton of iheyamine A, its subsequent transformation into the natural product was predicted to require facile redox chemistry. The route in Scheme 1 depicts the Beckmann rearrangement occurring first; the process could also commence with a Mannich cyclization followed by an intramolecular Beckmann rearrangement.

2. Results and discussion

In order to gauge the viability of the proposal outlined in



iheyamine A



iheyamine B

Fig. 1. Iheyamines A (**1**) and B (**2**).

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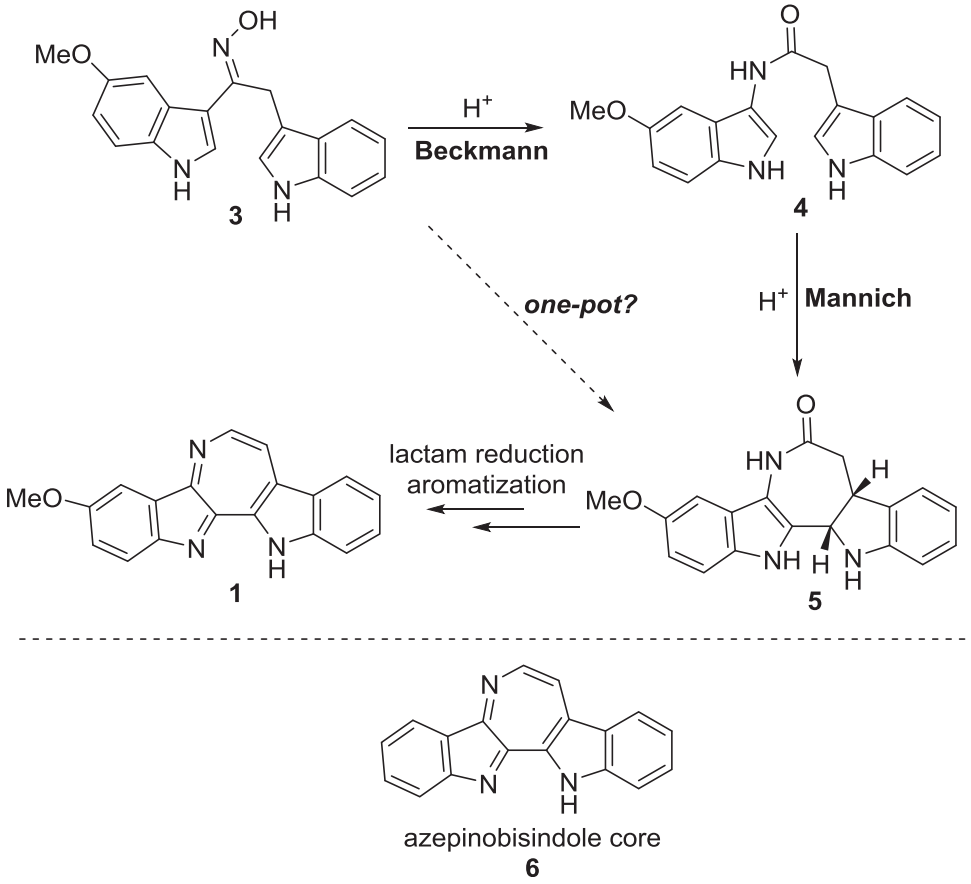
Scheme 1, a model study was initiated targeting the azepinobisindole core **6** of iheyamine A (Scheme 2). The known bis(indolyl) ketone **7**[6] was converted to the thermodynamically favoured (*E*)-**8**, with the oxime geometry confirmed by NOE analysis.[7] Given that both the Beckmann rearrangement and Mannich cyclization can be promoted by TFA,[3,4,8] we subjected (*E*)-**8** to TFA at room temperature in an effort to effect the proposed Beckmann-Mannich cascade, which led to the bisindolylacetamide **9** rapidly being formed. The product **9** is a result of the Beckmann rearrangement proceeding with the desired regioselectivity (migration of the *anti*-indole heterocycle), as confirmed by NOE analysis.[7] Upon subjecting the bisindolylacetamide **9** to TFA at 100 °C, the intramolecular Mannich reaction occurred to give the desired 2-(indolin-2-yl)indole **10**. Somewhat disappointingly, although the Beckmann rearrangement and Mannich cyclization both proceeded in neat TFA, we were unable to effect both of these reactions in a one-pot operation. For example, when the oxime **8** had undergone Beckmann rearrangement to **9** (as indicated by TLC analysis), heating the reaction to initiate the Mannich cyclization led to degradation.

The desired regiochemical outcome for the Mannich reaction (**9** to **10**) is worthy of comment and can be attributed to the choice of an amide (**9**) as the substrate for this reaction. This feature of the synthetic plan was guided by Bremner and co-workers' attempted biomimetic synthesis of the *N*-methyl iheyamine A core **11** (Scheme 3, **A**).[9] Bremner's approach required C–C bond migration to occur during the acid-mediated Plancher rearrangement[10,11] of spirocycle **11**, generating the carbocation **12** and hence the desired *N*-methylazepinobisindole **13**. However, C–N bond migration was favoured, resulting in the isomeric azepinobisindole **15**. In this instance, we posit the C–C bond migration did not occur as carbocation **12** is not resonance stabilised by the adjacent amine, which would be protonated under the reaction conditions. Conversely, C–N bond migration generated carbocation **14** stabilised by two aromatic systems. In our approach (Scheme 3, **B**), protonation of bisindolylacetamide **9** initiated an intramolecular Mannich cyclization to give the spirocycle **16** analogous to Bremner's intermediate **11**. In this instance, **16** undergoes C–C bond migration to give the desired 2-(indolin-2-yl)indole **10** via the carbocation **17**, which would experience resonance stabilization from the adjacent amide. C–N bond migration in **16** is also less favoured as carbocation **18** is only stabilised by one indole (compared to two in carbocation **14**) and as such, the undesired regioisomer **19** was not observed.

With the complete heterocyclic framework of the iheyamines assembled, we set out to convert 2-(indolin-2-yl)indole **10** into the azepinobisindole **6** using standard redox transformations (Scheme 4). This proved much harder than anticipated; attempted reduction of the lactam in **10** failed to give **20** when using a variety of reducing agents including lithium aluminium hydride, diisobutylaluminium hydride, borane and alane, a result that was attributed to the instability of compound **10**. It was thought that dehydrogenation of the indoline in **10** would give a more stable 2,2′-bisindole **21**, that upon lactam reduction would enable access to the azepinobisindole **6**. Despite careful treatment of **10** with one equivalent of DDQ, we were unable to prevent **22** being rapidly formed as a result of facile aromatization; the 2,2′-bisindole **21** was never observed. Subjecting **22** to the reducing agents described previously led to degradation and all attempts to access **6** from **22** via the imidoyl chloride[12] also failed.

The Beckmann-Mannich approach toward the synthesis of



Scheme 1. Proposed Beckmann-Mannich approach to iheyamine A (**1**).