Enantioselective Total Syntheses of Ircinal A and Related Manzamine Alkaloids

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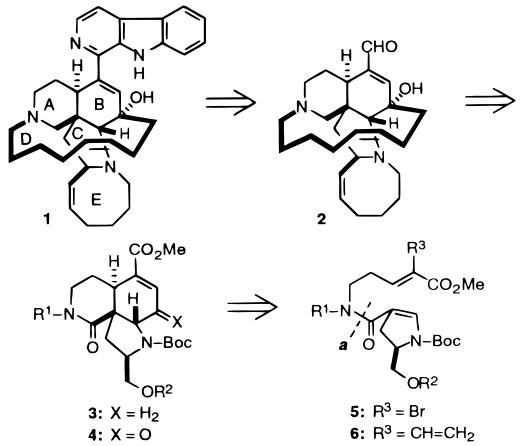
The manzamines constitute a growing family of structurally complex indole alkaloids that have been isolated from marine sponges of the genera *Haliclona* and *Pellina*, which are found off the coast of Okinawa.[1] Manzamine A (**1**), which exhibits potent antitumor activity in a number of assays,[2] was the first member of this group of alkaloids to be isolated. Subsequent to this exciting discovery, a number of related alkaloids including ircinal A (**2**), which was first converted into **1** by Kobayashi,[3] have been isolated. A novel biosynthetic pathway to the manzamine alkaloids has been proposed.[4] The combination of the complex and unusual structure of manzamine A and its promising biological activity has inspired numerous synthetic investigations,[5] one of which recently culminated in its synthesis.[6] Herein we report a concise enantioselective synthesis of ircinal A (**2**), and hence a formal synthesis of manzamine A (**1**), according to the overall plan outlined in Scheme 1. The key intermediate **5** is first assembled by coupling an unsaturated amino ester subunit with a chiral dienophilic subunit (disconnection ***a***). A novel domino Stille/Diels−Alder reaction is then marshaled to create the ABC tricyclic core **3** in a *single* operation from **5** via the triene **6**, which is generated *in situ*. Two sequential ring-closing metathesis (RCM) reactions are exploited to elaborate the requisite 13- and eight-membered rings leading to ircinal A (**2**).

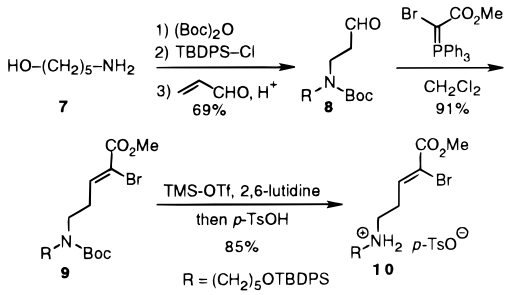
In early investigations, we had established the underlying viability of several key aspects of our strategy for the synthesis of ircinal A (**2**).[7] In particular, we had demonstrated that an intramolecular [4 + 2] cycloaddition of a dienic vinylogous imide related to **6** provided a facile entry to the ABC tricyclic core and that an RCM reaction of an α,ω-diene could be implemented to form the eight-membered *E* ring. However, the tetracyclic ABCE subunit thus prepared was not ideally endowed for transformation to **2**, and a modification of the approach was conceived that would provide a concise route to intermediates more readily amenable for conversion to ircinal A.

The synthesis commenced with the preparation of the diene precursor **10**, which bears a functionalized alkyl substituent on nitrogen that is suitable for eventual construction of the 13-membered ring. Thus, the amino alcohol **7** was converted into the protected amino aldehyde **8** in three steps (69% overall yield) by a sequence that featured the acid-catalyzed conjugate addition of a carbamate to acrolein.[8] Wittig olefination of **8** gave **9** in 91% yield together with small quantities (7%) of the *E*-isomer (Scheme 2). Removal of the nitrogen protecting group led to the tosylate salt **10** (85%) as a stable crystalline solid.[9]

Scheme 1



Scheme 2



The chiral dienophilic precursor **12** was prepared in >95% yield by a one-pot procedure involving the carboxylation and reduction of the known imide **11**,[7a] which was available in two steps (89%) from commercially available (5*S*)-5-(hydroxymethyl)-2-pyrrolidinone (Scheme 3). Although the carboxylic acid derived from **12** could be prepared, it was unstable and suffered facile decarboxylation, whereas the salt **12** could be stored without noticeable decomposition. Sequential reaction of **12** with oxalyl chloride (2.5 equiv) and then the free base of **10** in the presence of triethylamine afforded **13** (79% overall yield), thereby setting the stage for the critical domino Stille/Diels−Alder reaction. In the event, reaction of **13** with vinyl tributylstannane in the presence of Pd(0) afforded the triene **14** that spontaneously cyclized via an intramolecular Diels−Alder reaction to give solely **15** in 68% overall yield. In this novel sequence, the single stereocenter in **13** defines the absolute and relative stereochemistry at the remaining centers in the ABC ring subunit of **2**. Oxidation of the allylic methylene group in **15** proved somewhat troublesome and was best achieved by a modified Salmond protocol [CrO_3 (20 equiv), 3,5-dimethylpyrazole (30 equiv), CH_2Cl_2, rt, 48 h] that gave **16** in 63% yield (80% based upon recovered **15**).[10,11]

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(8) All new compounds were purified (>95%) by distillation, recrystallization, or preparative HPLC and were characterized by ^1H and ^{13}C NMR, IR, and HRMS.

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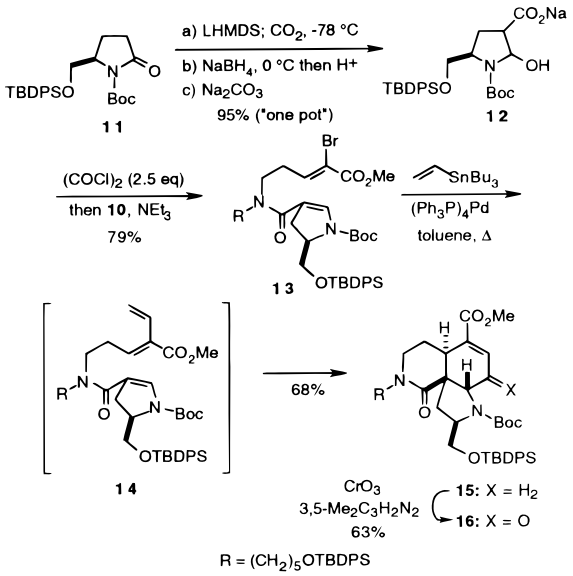
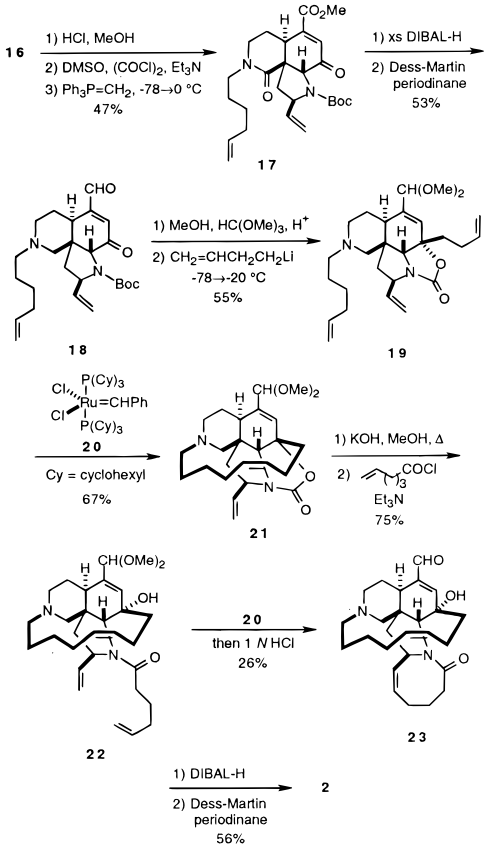
Scheme 3



In the next phase of the synthesis, the tricyclic subunit **16** was elaborated to set the stage for forming the 13- and eight-membered rings by sequential RCM reactions,[5b,7,12] and the sequence commenced with the parallel refunctionalization of the two protected primary alcohols (Scheme 4). Thus, deprotection of the two hydroxyl groups in **16** (84%) followed by Swern oxidation[13] of the intermediate alcohols furnished a dialdehyde (89%) that underwent a double Wittig reaction under salt-free conditions[14] to give **17** (63%). Global reduction of the carbonyl groups in **17** followed by oxidation of the two allylic alcohols thus produced with Dess−Martin periodinane[15] gave **18** in 53% overall yield. Selective protection of the aldehyde function of **18** as a dimethyl acetal (84%) followed by the stereoselective 1,2-addition of 4-butenyllithium[16] to the α,β-unsaturated ketone array (Et_2O/pentane, −78 °C → −20 °C; 65%) gave **19** in which the tertiary alcohol group is internally protected as a cyclic carbamate. When the diene **19** was exposed to the Grubbs ruthenium catalyst **20** (0.005 M in CH_2Cl_2, 0.13 equiv **20**, reflux, 3 h),[17] a facile RCM reaction ensued to furnish a mixture of geometric isomers (*Z*/*E* = ca. 8:1) from which **21** was isolated in 67% yield. In contrast to a previous observation in the literature, protonation of the tertiary amine in **19** prior to the RCM was not necessary.[18] Hydrolytic removal of the cyclic carbamate from **21** and *N*-acylation gave **22** (75% overall yield), which was characterized by X-ray crystallography. Although the 13-membered ring in **21** was readily formed by a RCM, the cyclization of the α,ω-diene array of **22** to generate the eight-membered *E* ring via a RCM was surprisingly problematic.[7] Under the best conditions identified thus far, we found that cyclization of **22** with the ruthenium catalyst **20** (0.004 M in C_6H_6, 1.1 equiv **20**, reflux, 30 min) followed by an aqueous acid workup to hydrolyze the dimethyl acetal moiety gave **23** in 26% yield.

Scheme 4



Reduction of **23** with DIBAL-H gave ircinol A (63%),[19] which was oxidized to ircinal A (**2**) (89%). The synthetic ircinal A gave a ^1H NMR spectrum that was identical with that of natural material, a ^{13}C NMR spectrum that matched the published data,[3] and a specific rotation that corresponded to previous reports {$[\alpha]_D$ = +48° (*c* = 0.07, $CHCl_3$); lit.[3] +48° (*c* = 2.9, $CHCl_3$); lit.[6] +46° (*c* = 0.23, $CHCl_3$)}. We did not have an authentic sample of ircinal A; therefore, to further validate the identity of synthetic **2**, a small quantity was converted into **1**, following the published protocol of Kobayashi.[3] The material thus obtained was identical (TLC, HPLC, ^1H NMR, HRMS) with a sample of natural manzamine A.

Thus, we have completed the enantioselective syntheses of ircinal A (**2**) and the related manzamine alkaloids ircinol A and manzamine A (**1**). The synthesis of **2** required a total of 24 operations from commercially available starting materials, and the longest linear sequence was 21 steps. This concise synthesis of ircinal A highlights a novel strategy for assembling the tricyclic ABC ring core by a domino Stille/Diels−Alder reaction, and it also demonstrates the power and versatility of RCM reactions for constructing 13- and eight-membered heterocyclic rings in highly functionalized settings.

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Supporting Information Available: Complete characterization (^1H and ^{13}C NMR and IR spectra and mass spectral data) for all new compounds, ^1H NMR spectra of synthetic and natural **2**, experimental procedures for preparing **15**, **19**, **21**−**23**, and **2**, and X-ray data for **22** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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