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Formal Syntheses of (±)-Pinnaic Acid and (±)-Halichlorine

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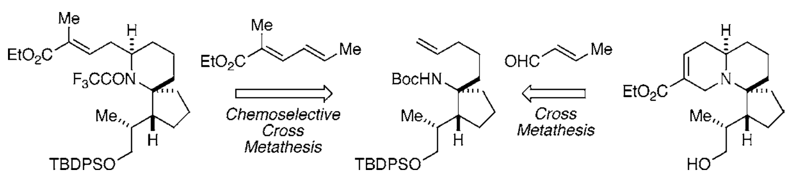
ABSTRACT



Concise formal syntheses of marine alkaloids (±)-pinnaic acid (1) and (±)-halichlorine (2) have been accomplished from a common intermediate. The syntheses illustrate the utility of selective olefin cross metathesis methodologies for the elaboration of advanced synthetic intermediates in complex molecule synthesis.

In 1996 Uemura and co-workers reported the isolation and structural characterization of two novel alkaloids. Pinnaic acid (**1**),[1] which was isolated from the Okinawan bivalve *Pinna muricata*, was found to be a specific inhibitor of cytosolic phospholipase A_2 (cPLA_2) with an in vitro IC_{50} of 0.2 mM. cPLA_2 is involved in regulating inflammation and thus represents a potential target for drug discovery. Halichlorine (**2**), which was isolated from the marine sponge *Halichondria okadai* Kadota (Figure 1),[2] inhibits the expression of vascular cell adhesion molecule-1 (VCAM-1) with an IC_{50} of 7 μg/mL and consequently has potential for the treatment of arteriosclerosis, asthma, and cancer.[3] As is evident from examination of their structures, both pinnaic acid and halichlorine possess several interesting features, one of which they have in common being the azaspiro[4.5]decane ring system.

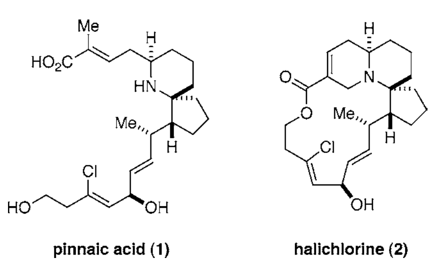


Figure 1. Structures of pinnaic acid (**1**) and (+)-halichlorine (**2**).

Because of their intriguing structures and biological activities, these alkaloids have attracted considerable attention in the synthetic community. However, although a rather large number of groups have published their respective approaches

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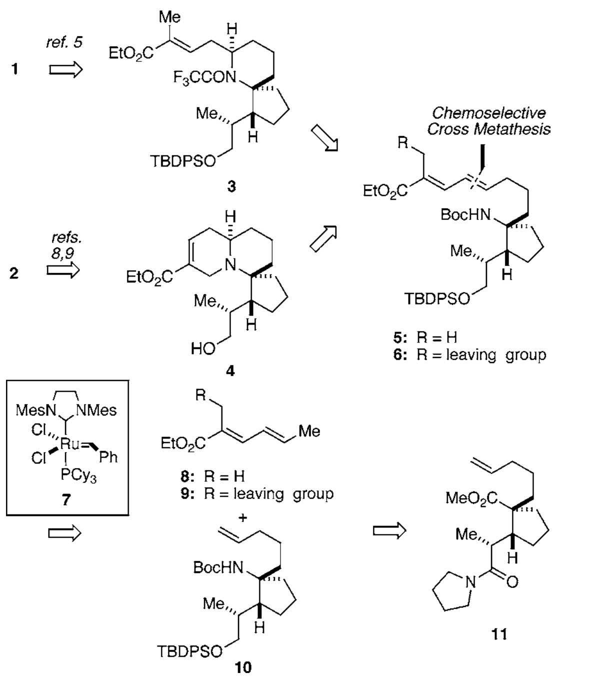
toward the assembly of the azaspirobicyclic and azaspirotricyclic cores,[4] only three total syntheses of **1**[5−7] and two total syntheses of **2** have been reported;[7,8] there have been two formal syntheses of **1** and **2**.[9,10]

Our approach to **1** and **2** was guided by a longstanding interest in developing new applications of olefin metathesis for the synthesis of complex natural products, particularly alkaloids.[11,12] We thus envisioned a unified strategy for the preparation of both of these alkaloids that would feature chemoselective cross metathesis reactions involving the key intermediate **10** (Scheme 1).

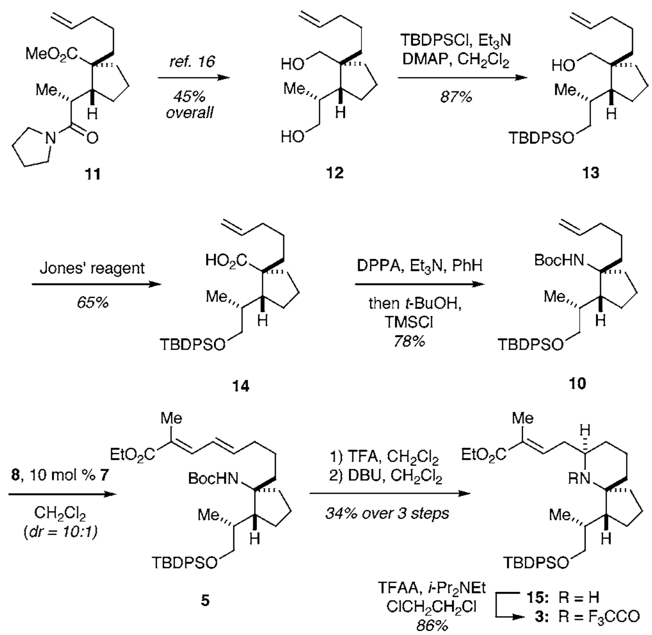
Scheme 1. Retrosynthesis of Pinnaic Acid (**1**) and Halichlorine (**2**)



A novel route to the diene **5**, a known intermediate that had been previously transformed into pinnaic acid (**1**) via **3**,[5] would entail a cross metathesis reaction between **10** and the dienoate **8**[13] in the presence of Grubbs' second generation metathesis catalyst (**7**).[14] Similarly, a cross metathesis reaction between **10** and a dienoate such as **9**, which bears a leaving group R, would lead to **6**, a possible intermediate en route to halichlorine (**2**). The opportunity to extend the scope of olefin cross metathesis[15] rendered this general approach to **1** and **2** particularly attractive. Olefin **10** would in turn be prepared by a Curtius rearrangement of a compound derived from **11**, whose synthesis via an efficient three-component reaction was reported by Heathcock.[16]

The formal synthesis of pinnaic acid (**1**) is summarized in Scheme 2. Selective silylation of the diol **12** with

Scheme 2. Formal Synthesis of Pinnaic Acid (**1**)



TBDPSCl, Et_3N, and catalytic DMAP afforded **13** in 87% yield. Jones oxidation of **13** furnished carboxylic acid **14**, which was subjected to a Curtius rearrangement with diphenyl phosphoryl azide (DPPA)[17] and *t*-BuOH to afford **10** in 51% yield for the two steps.

With the common intermediate **10** in hand, the stage was set for the pivotal cross metathesis reaction. Heating a mixture of **10** and dienoate **8** under reflux (CH_2Cl_2) for 3 h in the presence of Grubbs II catalyst (**7**) (10 mol %) provided an inseparable mixture of **5** and the dimer of **8**.[18,19] Pure **5** (*E*/*Z* = 10:1) could be obtained by a sequence of reactions involving removal of the *N*-Boc group, purification of the intermediate amine, and reinstallation of the *N*-Boc group (29% overall yield). Owing to the inefficiency of this process and practical considerations, we decided to telescope three reactions. In the event, the azaspirobicycle **15** was prepared

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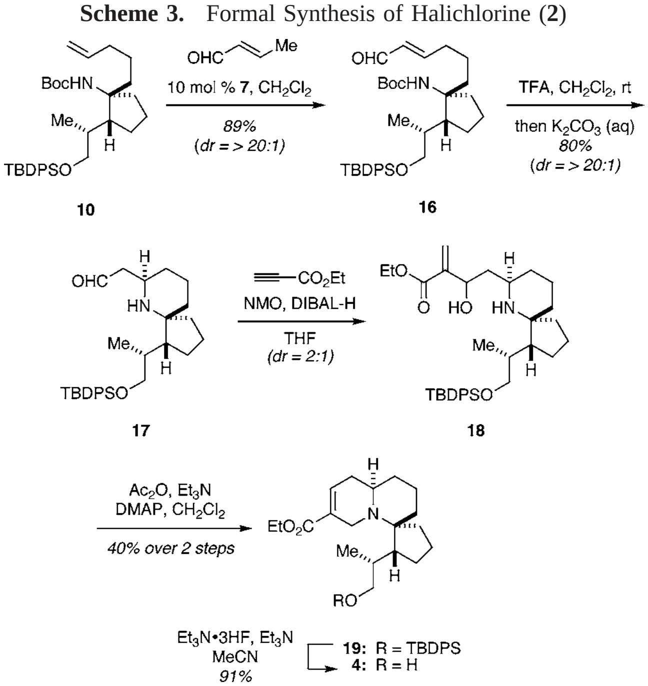
in 34% overall yield via chemoselective cross metathesis of **8** and **10**, followed by removal of the *N*-Boc group and cyclization of the intermediate amino dienoate via intramolecular 1,6-conjugate addition. Subsequent protection of **15** as its trifluoroacetamide derivative afforded **3**.[5a] Spectral data of **3** were consistent with those reported by Kibayashi.[9] Inasmuch as **3** had been previously converted into pinnaic acid (**1**) by Danishefsky,[5b] the preparation of **3** in 11 steps (5.8% overall yield) starting from commercially available methyl 1-cyclopentene-1-carboxylate completes a formal synthesis of **1**.

The application of a different cross metathesis to the formal synthesis of halichlorine (**2**) was then explored. While we were able to access structures of the general type **6**,[20] cyclizations of amines obtained upon *N*-deprotection of such compounds via intramolecular 1,6-conjugate addition were problematic, perhaps owing to competing elimination pathways. Although such conversions are still being explored, an alternative route to **4** was developed.

We discovered that the cross metathesis reaction of **10** with crotonaldehyde proceeded in 89% yield with excellent diastereoselectivity (>20:1 *E/Z* ratio) (Scheme 3). When this

Scheme 3. Formal Synthesis of Halichlorine (**2**)



cross metathesis reaction was performed with acrolein, the more common coupling partner for this transformation, lower yields (30−35%) were consistently obtained with the bulk of the mass balance being unreacted olefin **10**. Thus, the use of crotonaldehyde in such constructions provides a significant advantage.

Removal of the *N*-Boc group of **16** with TFA followed by neutralization at 0 °C with aqueous K_2CO_3 triggered an aza-Michael cyclization to furnish aldehyde **17** in 80% yield (dr = >20:1). The observed diastereoselectivity in this reaction was consistent with findings by Danishefsky in a similar system.[21]

Developing an efficient and new means of transforming **17** into **19** represented a significant challenge. Among several tactics that were explored, we considered that **18** might serve as a useful intermediate. Although the Baylis−Hillman reaction might seem well-suited to such a construction,[22] neither it nor its many variants delivered **18** in acceptable yield. On the other hand, recruitment of Ramachandran's vinylalumination methodolgy[23] delivered **18** as an inconsequential mixture of diastereomers (dr = 2:1). Acetylation of this mixture under standard conditions led to a facile cyclization that provided the known tricycle **19**[9] in 40% overall yield.[24] Treatment of **19** with triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$)[25] removed the silyl ether moiety to furnish **4** in 91% yield. Spectral data of **4** were consistent with those reported by Kibayashi in his formal synthesis of halichlorine (**2**).[9] Thus, the synthesis of **4** in 12 linear steps (5.1% overall yield) starting from commercially available methyl 1-cyclopentene-1-carboxylate constitutes a formal synthesis of **2**.

In summary, concise formal syntheses of pinnaic acid (**1**) and halichlorine (**2**) have been accomplished by intercepting the known intermediates **3** and **4**, respectively. The unified strategy for preparing **3** and **4** highlights the utility of olefin cross metathesis methodologies for the efficient construction of key olefinic bonds in the arena of natural product synthesis. Other applications of olefin metathesis to solving problems in total synthesis are under active investigation, and the results of these studies will be disclosed in due course.

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Supporting Information Available: Experimental procedures for **3**−**5**, **10**, **13**−**19** and ^{1}H spectra for **3**−**5**, **10**, **13**−**17**, **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Initial experiments with ethyl 2-methyl-2,4-pentadienoate as the diene component in the cross metathesis also provided **5**, albeit in slightly lower yield. Small amounts of the homodimer of **10** were sometimes observed but not under the conditions reported herein. No other products derived from **10** could be isolated and characterized.

(20) The cross metathesis reaction of **10** and **9** (R = OAc) (10 mol % **7**, CH_2Cl_2, reflux, 3 h) afforded **6** (R = OAc) in 59% yield (>10:1 *E/Z* ratio).

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