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An in situ iminium formation–allylation approach towards the 1-aza-[4.5.0]-spirobicyclic core of halichlorine and pinnaic acid

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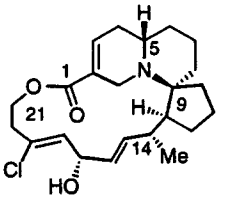
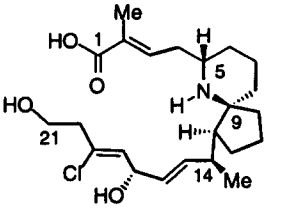
Abstract

A facile procedure for the formation and allylation α to the nitrogen of 1-azaspirobicyclic systems has been developed. In examining an approach towards the synthesis of the natural products halichlorine (**1**) and pinnaic acid (**2**), spontaneous condensation of an aldehyde-carbamate to form a spirobicyclic *N*-acylenamine was observed. Introduction of the C1–C5 moiety of the natural products was then initiated in a one pot procedure involving acid mediated enamine–imine conversion and treatment with allyltrimethylsilane. This resulted in essentially a single diastereomeric product, which was determined to correspond to the C5 epimer of **1** and **2**.

Halichlorine (**1**), and pinnaic acid (**2**) are two structurally related natural products isolated from the sponge *Halichondria okadai*[1,2] and the marine bivalve *Pinna muricata*,[3] respectively, by Uemura and co-workers. Due to their unusual structures and interesting biological activities these compounds have begun to attract the interest of the synthetic community.[4–6] Both **1** and **2** share highly functionalized 1-aza-[4.5.0]-spirobicyclic ring systems, which present the main synthetic challenge towards these unique natural products.



Halichlorine (1)



Pinnaic acid (2)

An initial synthetic approach towards the spirobicyclic core of **1** and **2** was envisioned to involve an intramolecular hetero-Michael reaction of amino-acrylate **4**, to result in the spirobicylic compound

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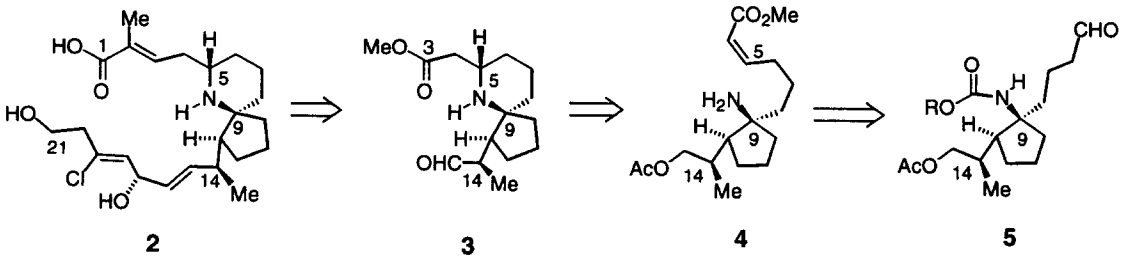
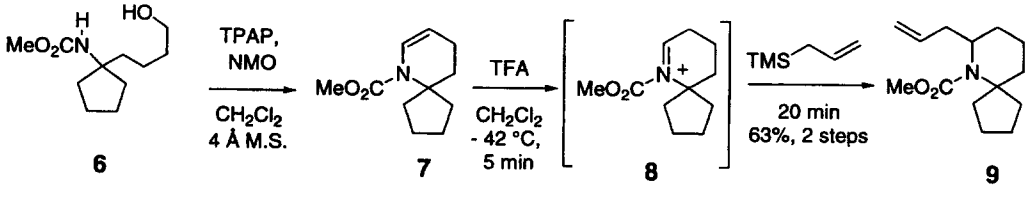
3 (Scheme 1). The natural products' relative configuration at the newly formed C5 stereogenic center of 3 was expected to be favored thermodynamically, whereas a kinetic preference of hetero-Michael addition might be affected by choice of (*E*) versus (*Z*) configuration of the pendant acrylate in 4.[7–9] Further elaboration involving installation of the C1–C2 and C15–C21 side chains would then lead to 2. Acrylate 4 was to arise from carbamate-aldehyde 5, which bears the essential stereochemical triad about the cyclopentane ring. However, during preliminary examination of this synthetic plan, in situ condensation of an aldehyde-carbamate occurred, which prompted the development of a more interesting route to elaborate the functionalized spiroamine core of 1 and 2.



Scheme 1.

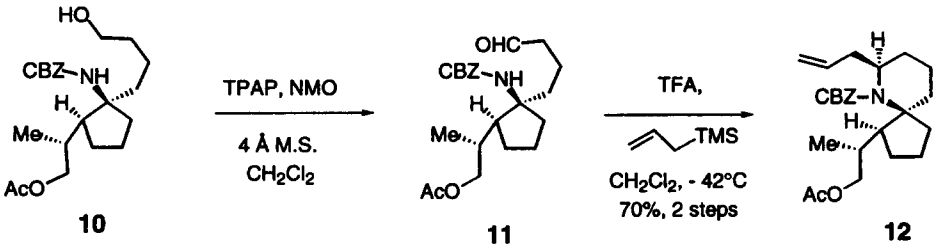
The simple model alcohol-carbamate 6 (Scheme 2) lacking the C14 side chain of the natural products was prepared and subjected to oxidation in order to provide the corresponding aldehyde as a prelude to acrylate installation. Instead, oxidation of 6 with TPAP/NMO led to spontaneous condensation to the unstable *N*-acylenamine 7. Functionalization of the enamine α-carbon would then be required for installation of the C1–C4 side chain. Several methods for accomplishing this general type of transformation have been reported previously, including Corey's use of an acid-mediated intramolecular condensation of a methyl ketone/enamine in the synthesis of (±)-porantherine,[10] and, more recently, an indium-mediated α-allylation of enamines with allyl bromide.[11] Here, it was envisioned that protonation of the enamine would result in an iminium ion, which could be trapped stereoselectively by an allylic silane. Allylations of iminium ions are well precedented,[12,13] but it would be particularly advantageous here to form and stereoselectively functionalize the highly substituted piperidine ring in only two operations from the carbamate-alcohol.



Scheme 2.

To test the feasibility of stereoselective enamine α-allylation via an in situ derived iminium ion (8), the crude enamine 7 was treated with TFA at –42°C in CH_2Cl_2 for 5 min before allyltrimethylsilane was added (Scheme 2). Allylation was clean and complete within an additional 20 min, resulting in the α-allylation product 9 in 63% yield from 7. Overall, this sequence of oxidative *N*-acylenamine formation, acid-induced iminium formation and allylation provided a useful method for the formation of the allyl substituted 1-aza-[4.5.0]-spirobicyclic ring system (e.g. 9) representing the spirobicyclic core and C1–C4 side chain precursor of 1 and 2. However, in this simple model system it was not possible to study the stereoselectivity of the carbon–carbon bond forming step.

This sequence was then applied to a more highly functionalized synthetic intermediate (±)-**10**[14] (Scheme 3). In the presence of the benzyl carbamate in this case, enamine formation was not spontaneous under the TPAP oxidation conditions. However, treatment of crude aldehyde **11** under the TFA reaction conditions led to condensation and iminium ion formation. Interestingly, upon addition of allyltrimethyl silane to this in situ prepared iminium ion, the allyl addition product **12** was isolated as a *single diastereomer.*



Scheme 3.

The relative stereochemistry of **12** was determined by NOE studies which were performed on the derived acrylate (Fig. 1). The C1–C4 side chain corresponding to **1** was elaborated by oxidation of the alkene in **12** followed by Wittig olefination to give **13**. In contrast to the NOEs that were reportedly observed between the protons at C5 and those at C10 and C7 in **2**,[3] NOEs were observed between protons at C4 and C10, and between those at C5 and the methyl group at C14 of **13**. Hence, the relative configuration at C5 in **13** and **12** was determined to be epimeric to that of **1** and **2**.

The stereoselectivity of allylation is consistent with allyl attack occurring on the axial face (A) of an iminium ion **14e**, or on the equatorial face (*E*) of iminium conformer **14a** (Scheme 4).[15] The former would be favored stereoelectronically,[15] whereas attack upon either iminium conformer **14e** or **14a** from the α-face to result in the unobserved (5*S**,9*S**) diastereomer would be either stereoelectronically or sterically disfavored, respectively. Although **14a** has the sterically larger C13 substituent in a pseudoaxial position, this conformer may reduce $A_{1,3}$-strain between the C13 substituent and the carbamate moiety. Although the stereoselectivity observed here is readily explained, it does not lead directly to the natural product targets **1** and **2**. It is noteworthy that concurrent with these studies, Ariomoto and co-workers reported obtaining similar facial selectivity upon *hydride* delivery to a *ketone*-derived iminium species analogous to **14**, which successfully installs the correct relative stereochemistry required for **1** and **2**.[4]

In summary, the in situ formation and stereoselective allylation of cyclic iminium species reported here represents a facile reaction sequence for the synthesis of substituted cyclic *N*-acylamine derivatives from acyclic carbamates. Further applications of this methodology to the stereoselective synthesis of spirobicyclic amine-containing compounds are continuing and will be reported in due course.

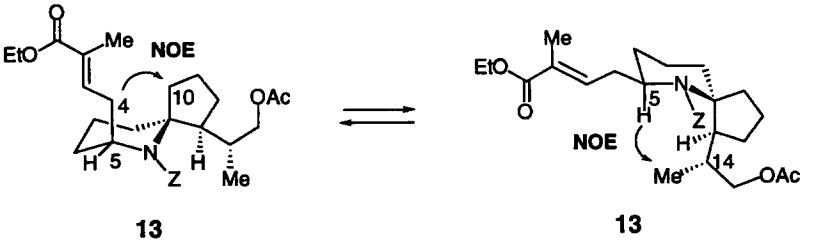
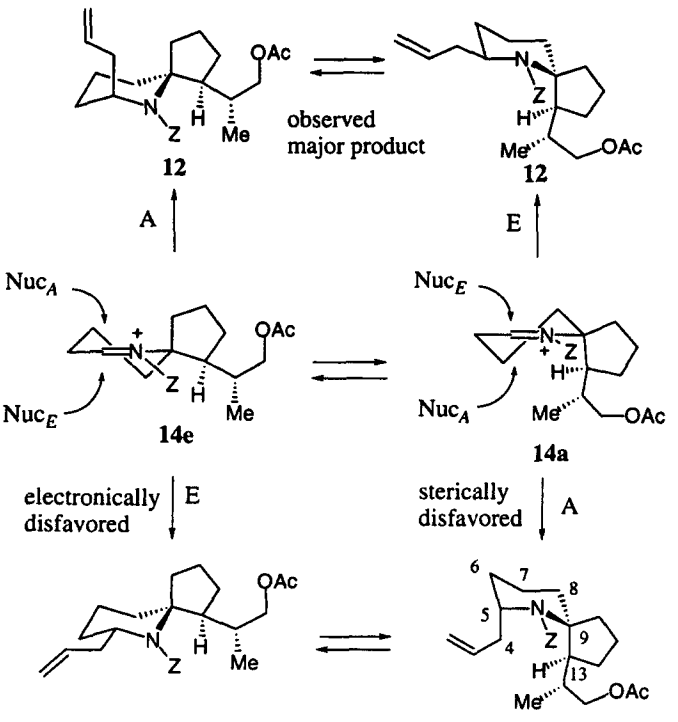


Figure 1. Diagnostic NOEs observed in the acrylate **13**



Scheme 4.

Acknowledgements

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