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Formal Total Synthesis of the Cytotoxic Marine Ascidian Alkaloid Haouamine A

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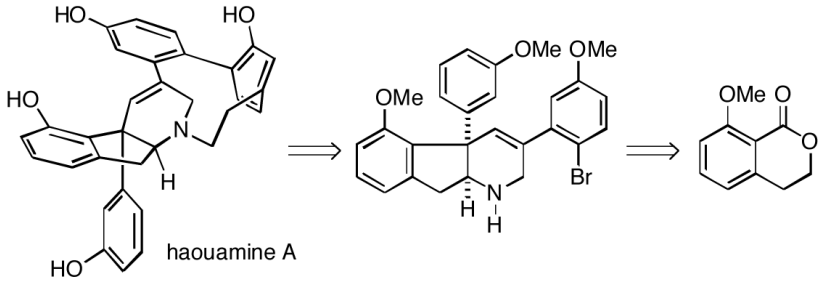
Abstract



Described is a convergent 13-step synthesis of a pentacyclic compound which has previously been transformed into haouamine A, therefore constituting a formal total synthesis of this unique marine alkaloid.

In 2003, Zubia and coworkers isolated two novel polycyclic alkaloids from the marine ascidian *Aplidium haouarianum* collected off the southern coast of Spain.[1] The compounds were named haouamine A and B, and were assigned structures **1** and **2**, respectively, based upon NMR analysis and X-ray crystallography. Interestingly, these metabolites exist in solution as a dynamic 2:1 interconverting mixture of stereoisomers generated either by nitrogen inversion or by atropisomerism of the paracyclophane system. A unique feature of these alkaloids is the 3-aza-[7]-paracyclophane moiety, which is so highly strained that the B-ring is in fact non-planar and exists in a boat-like conformation, as can be seen from the X-ray structure. The absolute configuration of these metabolites has not yet been established. Haouamine A has high and selective activity against the human colon carcinoma cell line HT-29 with an IC_{50} of 0.1 μg/mL. Haouamine B has only slight cytotoxic activity against mouse endothelial cells MS-1.

During the past year several research groups have begun to address the synthesis of the haouamines.[2] Rawal and coworkers,[2a] and Grundl and Trauner[2b] have devised nice approaches to the indenotetrahydropyridine nucleus of the alkaloids. More recently, Wipf and Furegati have reported that the very strained aza-paracyclophane system of the haouamines cannot be constructed by standard biaryl coupling methodology.[2c] However, they were able to prepare a haouamine 3-aza-[7]-paracyclophane model system via a late stage aromatization of a non-benzenoid B-ring precursor.

In 2006, Baran and Burns published the first total synthesis of haouamine A (**1**).[3] In the course of this work it was also found that metal-mediated biaryl coupling technology cannot be used to generate the paracyclophane. A clever solution to this problem was to convert intermediate

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aryl bromide **3** to α-pyrone alkyne **4**, which upon heating underwent an intramolecular Diels-Alder reaction to produce cycloadduct **5** (Scheme 1). Subsequent spontaneous loss of carbon dioxide from adduct **5** gave tetraacetyl-haouamine A (albeit in low conversion from **4**) which could be transformed to the alkaloid **1**.

In this communication we describe a new and efficient approach to the Baran indenotetrahydropyridine pentacyclic intermediate **3**, which therefore constitutes a formal total synthesis of haouamine A. Our strategy for construction of **3** was to use an intramolecular nitrone/olefin dipolar cycloaddition to produce the requisite indene system with its attendant functionality and stereochemistry.[4,5] The initial plan was then to utilize the ring closing metathesis chemistry of vinyl chlorides which we had previously developed to establish the tetrahydropyridine ring.[6]

To prepare the intermediate necessary for the nitrone/olefin cycloaddition, we began with known, readily prepared lactone **6**,[7] which underwent addition of commercially available Grignard reagent **7** to afford keto alcohol **8** in high yield (Scheme 2). This alcohol was protected as silyl ether **9**. Olefination of ketone **9** could be effected cleanly with the Tebbe-Petasis reagent[8,9] to give **10**, and subsequent removal of the silyl group afforded alcohol **11**. Finally, Dess-Martin oxidation[10] of alcohol **11** generated aldehyde **12**.

With this aldehyde in hand, we began to explore the proposed intramolecular nitrone/olefin dipolar cycloaddition. Treatment of aldehyde **12** with *N*-benzylhydroxylamine in toluene at room temperature for one hour produced nitrone **13**, as monitored by ^{1}H NMR (Scheme 3). Subsequent heating of the solution of **13** at 115 °C for 36 hours, followed by column chromatography, produced the desired linear cycloadduct **14** in 63% isolated yield. The structure and stereochemistry of this isoxazolidine was confirmed by NMR and X-ray analysis. In addition to adduct **14**, an impure chromatographic fraction was isolated which contained the bridged cycloadduct **15**, but despite some effort, this compound could not be obtained in pure form for full characterization. However, heating the fraction containing **15** in toluene at 115 ° C for 24 h produced the linear adduct **14**, increasing the overall yield to 76%. This process undoubtedly involves a well precedented thermal retro-cycloaddition of the bridged adduct **15** to starting nitrone **13**.[4,5] In view of these results, the cycloaddition was conducted in toluene-d_8 in an NMR tube, and was periodically monitored. It was found that bridged cycloadduct **15** is the kinetic product of the reaction, and over time is converted to the more stable linear adduct **14**. For preparative purposes, it proved most convenient to heat the nitrone **13** in toluene solution in an oil bath maintained at 130 °C for 45 hours, which provided the desired adduct **14** in 73% isolated yield after chromatography.

As noted above, our original intent was to construct a functionalized tetrahydropyridine ring potentially useful for the haouamines via a ring closing metathesis of a vinyl chloride.[6] Towards this end, isoxazolidine **14** was first hydrogenated with Pearlman's catalyst to afford amino alcohol **16** (Scheme 4). Protection of this alcohol as the TBS ether **17**, followed by conversion of the amine to the trifluoroacetamide and removal of the silyl group led to alcohol **18**. Dess-Martin oxidation[10] of alcohol **18** to the corresponding aldehyde and subsequent Peterson olefination then afforded intermediate **19**. All attempts to directly *N*-alkylate the anion derived from trifluoroacetamide **19** with 3-iodo-2-chloropropene failed.[11] Therefore, it was necessary to first remove the trifluoroacetyl group to generate the corresponding free amine, which could be successfully alkylated to yield diene amine **20**. Reintroduction of the TFA protecting group gave the desired metathesis substrate **21** in high overall yield. Unfortunately, all attempts to effect ring closing metathesis of **21** to produce indenotetrahydropyridine **22** failed despite screening a number of catalysts. In most cases only the starting diene **21** was recovered. We believe the problem here is steric in origin, since based upon our earlier work

it appears that the non-chlorinated olefin must initially form a metal carbene species for this RCM process to occur as desired.[6]

Since the metathesis strategy proved untenable, we turned to what proved to be a shorter and more convergent approach for introducing both the tetrahydropyridine and A-rings. It was possible to couple amine **17** with known phenylacetic acid **23**[12] leading to amide **24** (Scheme 5). Removal of the silyl protecting group of **24** with TBAF followed by Dess-Martin oxidation[10] of the resulting primary alcohol afforded aldehyde **25**. In a key transformation, it was found that warming aldehyde amide **25** in warm methanol in the presence of potassium carbonate effects an aldol condensation/dehydration to produce the desired pentacyclic lactam **26** in high yield. To complete the synthesis, lactam **26** was reduced with lithium aluminum hydride/zinc chloride to give the Baran pentacycle **3** in good yield.[13] This compound has spectral data identical to those previously reported.[3]

In conclusion, we have developed a convergent synthesis of the Baran pentacycle **3** which requires 13 steps and proceeds in 34% overall yield starting from readily available bicyclic lactone **6**. We are currently investigating some new strategies for efficiently converting this intermediate into haouamine A (**1**).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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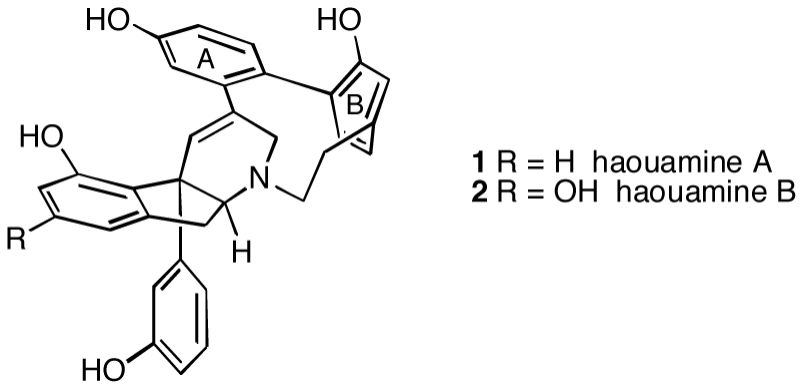
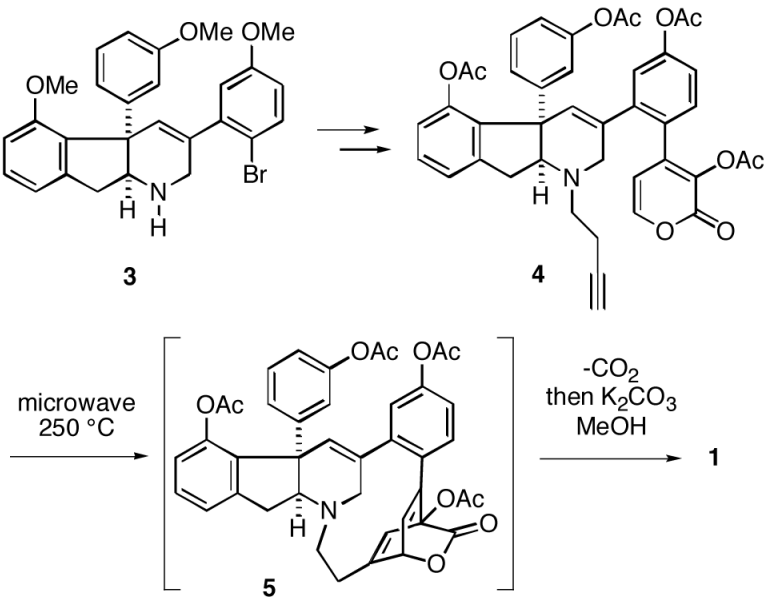
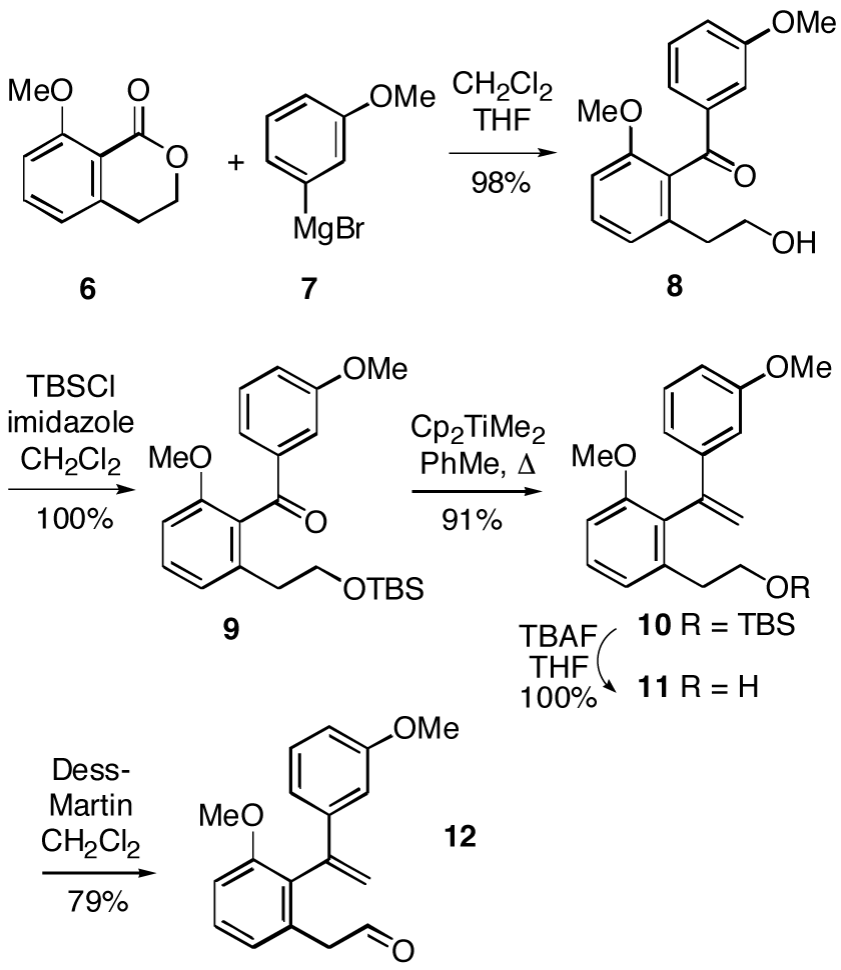


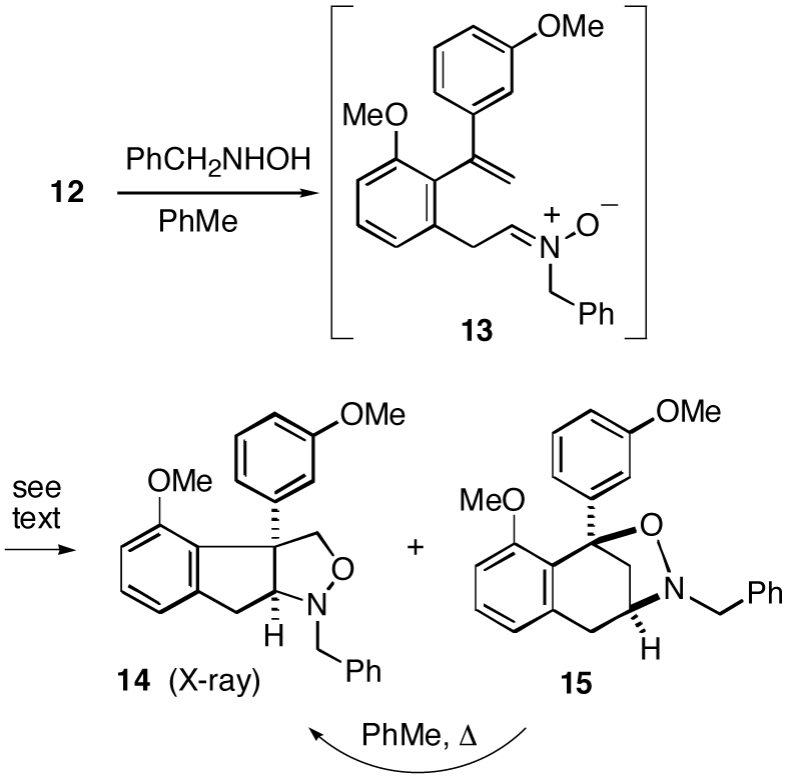
Figure 1.
Structures of haouamines.



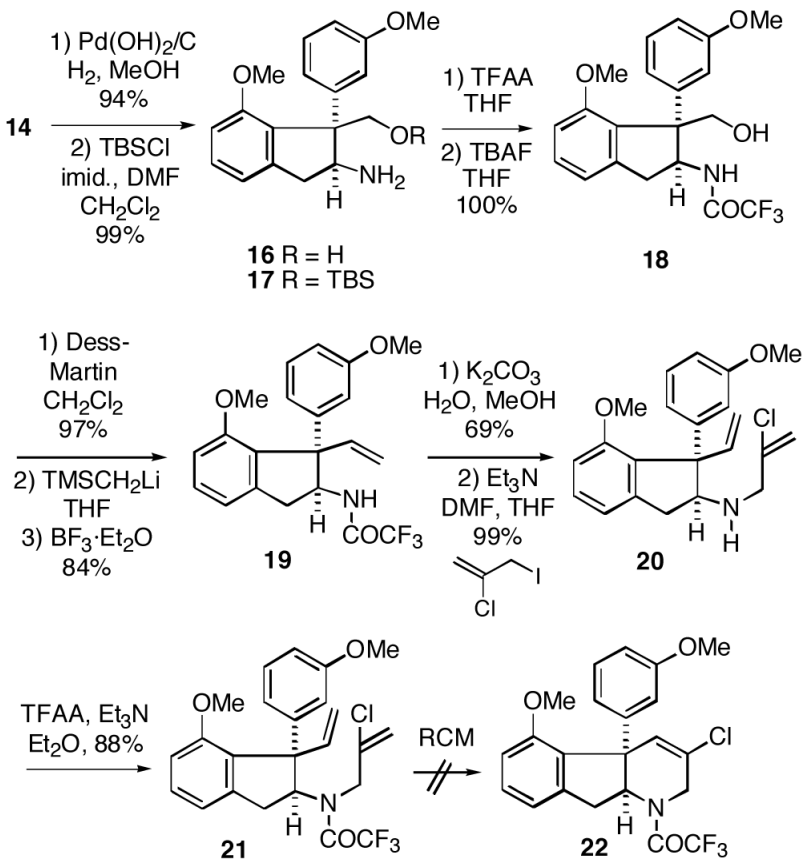
Scheme 1.



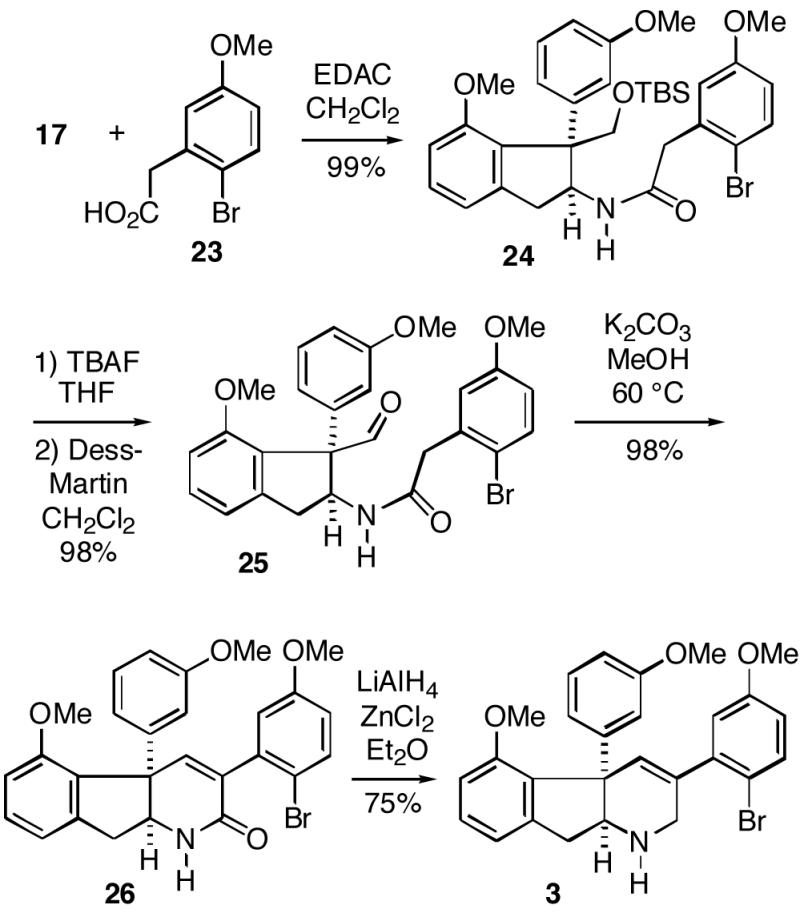
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.