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Formal Total Synthesis of the Cytotoxic Marine Ascidian Alkaloid Haouamine A

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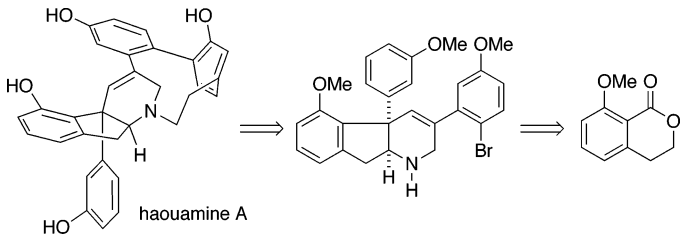
ABSTRACT



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 co-workers 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, on the basis of NMR analysis and X-ray crystallography (Figure 1). Interestingly, these

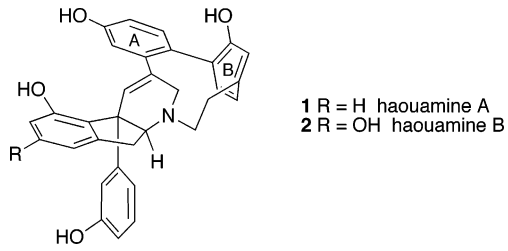


Figure 1. Structures of haouamines.

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 nonplanar and exists in a boatlike 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 co-workers[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 the 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 nonbenzenoid 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

(1) Garrido, L.; Zubia, E.; Ortega, M. J.; Salva, J. *J. Org. Chem.* **2003**, *68*, 293.

(2) (a) Smith, N. D.; Hayashida, J.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 4309. (b) Grundl, M. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 23. (c) Wipf, P.; Furegati, M. *Org. Lett.* **2006**, *8*, 1901.

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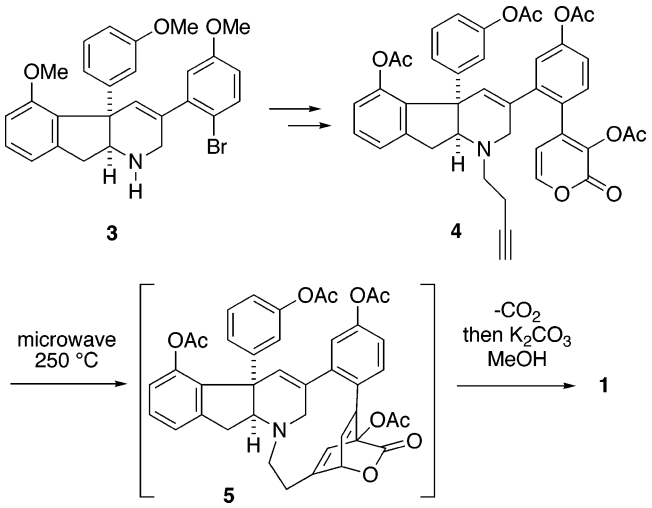
found that metal-mediated biaryl coupling technology cannot be used to generate the paracyclophane. A clever solution to this problem was to convert intermediate aryl bromide **3** to α-pyrone alkyne **4**, which upon heating underwent an intramolecular Diels−Alder reaction to produce cycloadduct **5** (Scheme 1). Subsequent spontaneous loss of carbon dioxide

Scheme 1

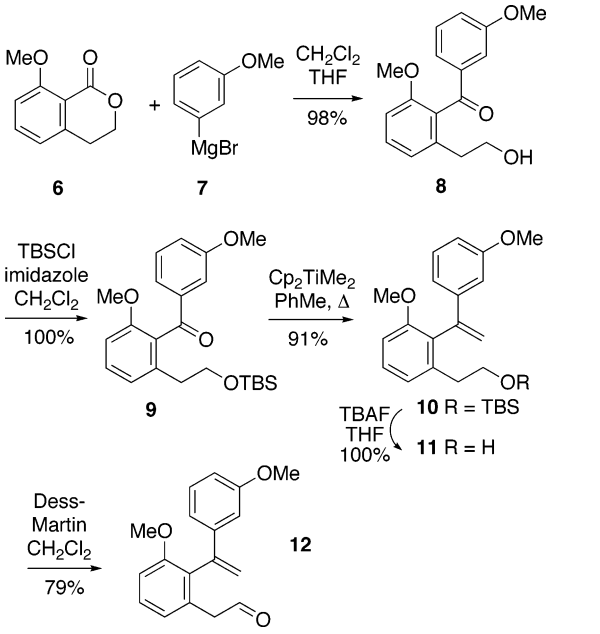


from adduct **5** gave tetraacetyl-haouamine A (albeit in low conversion from **4**) which could be transformed to the alkaloid **1**.

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 the 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]

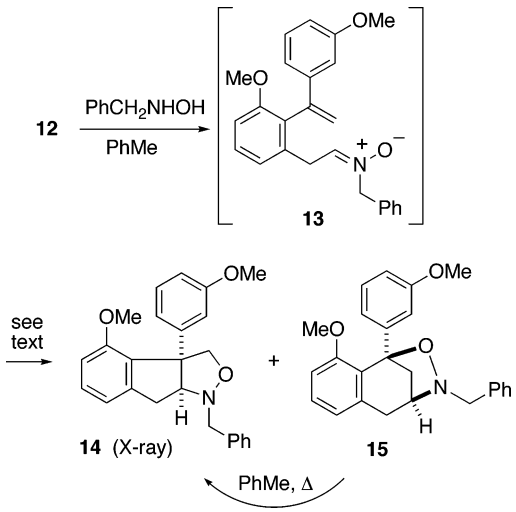
To prepare the intermediate necessary for the nitrone/olefin cycloaddition, we began with known, readily prepared lactone **6**,[7] which underwent addition of commercially available Grignard reagent **7** to afford keto alcohol **8** in high yield (Scheme 2). This alcohol was protected as silyl ether **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**.

Scheme 2



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 1 h produced nitrone **13**, as monitored by ^{1}H NMR (Scheme 3). Subsequent heating of

Scheme 3



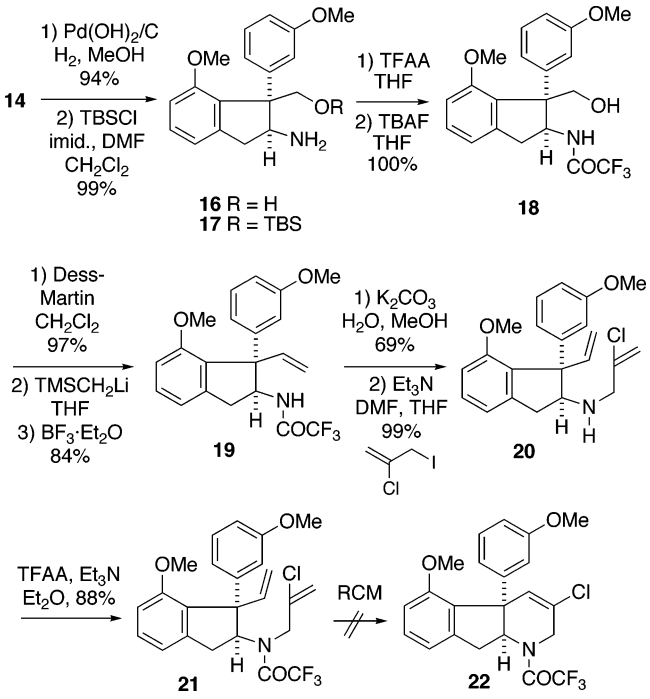
the solution of **13** at 115 °C for 36 h, followed by column chromatography, produced the desired linear cycloadduct **14** in 63% isolated yield. The structure and stereochemistry of

(3) Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc*. **2006**, *128*, 3908.
(4) Cf.: Baldwin, S. W.; Debenham, J. S. *Org. Lett*. **2000**, *2*, 99.
(5) For a recent review of nitrone/olefin cycloadditions, see: Jones, R. C. F.; Martin, J. N. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002; Chapter 1.
(6) (a) Chao, W.; Weinreb, S. M. *Org. Lett*. **2003**, *5*, 2505. (b) Chao, W.; Meketa, M. L.; Weinreb, S. M. *Synthesis* **2004**, 2058.
(7) Rama Rao, A. V.; Reddy, D. R. *Synth. Commun*. **1986**, *16*, 97.
(8) (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc*. **1990**, *112*, 6392. (b) Payack, J. F.; Hughes, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. *Org. Synth*. **2002**, *79*, 355.
(9) This methylenation cannot be done by Wittig chemistry, and the Peterson reaction proceeds in poor yield. However, alkene **10** can also be prepared from ketone **9** in a yield similar to that for the Tebbe−Petasis reaction by addition of methyllithium, followed by dehydration with hot acetic acid.
(10) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277.

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 retrocycloaddition 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 h, 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] Toward 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

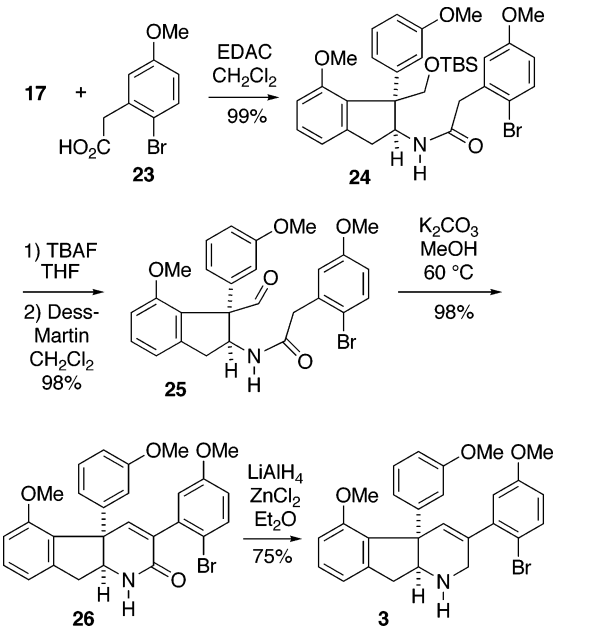
Scheme 4



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 because based on our earlier work it appears that the nonchlorinated olefin must initially form a metal carbene species for this RCM process to occur as desired.[6]

Because 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).

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

(11) Nordlander, J. E.; Catalane, D. B.; Eberlein, T. H.; Farkas, L. V.; Howe, R. S.; Stevens, R. M.; Tripoulas, N. A. *Tetrahedron Lett.* **1978**, 4987.
(12) Lebegue, N.; Bethegnies, G.; Berthelot, P. *Synth. Commun.* **2004**, *34*, 1041.
(13) Van der Veken, P.; Kertesz, I.; Senten, K.; Haemers, A.; Augustyns, K. *Tetrahedron Lett.* **2003**, *44*, 6231.

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**).

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Supporting Information Available: Experimental procedures for the preparation of new compounds including X-ray data and copies of NMR spectra. This material is available free of charge on the Internet at http://pubs.acs.org.

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