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A Concise Route to the Azaspirodecane Moiety of Halichlorine and Structurally Related Alkaloids

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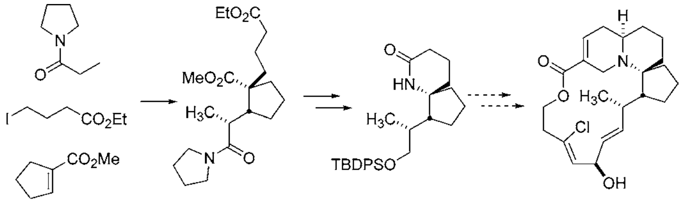
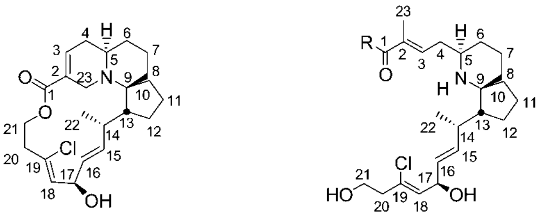
ABSTRACT



(±)-halichlorine

A tandem Michael addition–enolate alkylation followed by Dieckmann cyclization and Beckmann rearrangement provided the corresponding [5.4.0] azaspirobicyclodecane, a key intermediate in our synthetic route to the marine alkaloid halichlorine (1).

The marine alkaloid halichlorine (**1**) (Figure 1) was isolated from the marine sponge *Halichondria okadai* Kadota in 1996 by Uemura and co-workers.[1] The structurally related natural products, pinnaic acid (**2**) and tauropinnaic acid (**3**), were isolated by the same research group from the Okinawan bivalve *Pinna muricata*.[2] Their complex spirobicylic structures and multiple biological properties including potential activity against heart disease (halichlorine), inflammation, and other disease states (pinnaic and tauropinnaic acids) and limited availability from natural sources have prompted many research groups to search for synthetic approaches, particularly for the common azaspirobicyclic core.[3] To the best of our knowledge, only two total syntheses of halichlorine,[4] three of pinnaic acid,[4c,5] and one of tauropinnaic acid[4c] have been reported so far in the literature. Here we disclose our



halichlorine (1)

pinnaic acid (2) R = OH

tauropinnaic acid (3) R = NHCH$_2$CH$_2$SO$_3$H

Figure 1. Halichlorine (**1**), pinnaic acid (**2**), and tauropinnaic acid (**3**).

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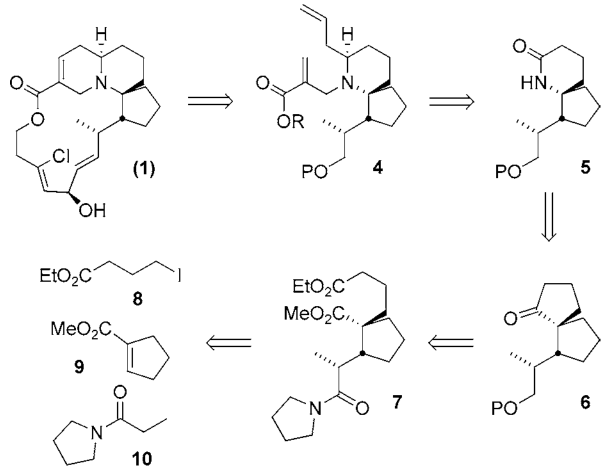
results on the preparation of the common azaspirodecane **19** through a short and stereoselective route.

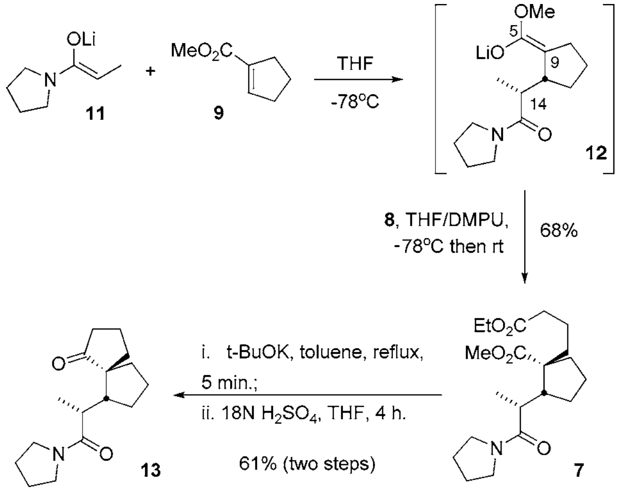
Our retrosynthetic analysis for halichlorine (**1**) is depicted in Scheme 1. We envisioned that the azaspirocyclic core **5** could be reached via Beckmann rearrangement of ketone **6**, constructed via Dieckmann condensation, followed by decarboxylation from diester **7** which was planned to be prepared by a tandem Michael addition/enolate alkylation of 1-carbomethoxycyclopentene (**9**).

Scheme 1. Retrosynthetic Analysis of Our Approach to Halichlorine (**1**), Pinnaic Acid (**2**), and Tauropinnaic Acid



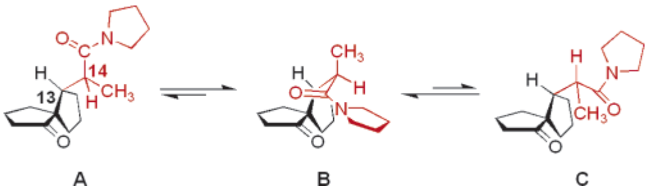
To put our plans into practice, intermediate **7** was prepared following a modification of the procedure successfully implemented by Heathcock and co-workers in their syntheses of *Daphniphyllum* alkaloids (Scheme 2).[6] *Z*-Enolate **11**, generated from *N*-propionyl pyrrolidine (**10**) and LDA,[7] reacted with 1-carbomethoxycyclopentene (**9**) to give enolate **12**, which was trapped in situ by iodide **8** to yield **7** in 68% yield as the major stereoisomer. Its relative configuration was assigned based on the stereochemical outcome of the analogous transformation previously reported by Heathcock and co-workers.[6] Amide **7** was submitted to basic conditions in order to afford the corresponding Dieckmann adduct, followed by exposure to concentrated sulfuric acid to promote its decarboxylation to yield amide **13** in 61% yield for two steps.

Scheme 2. Synthesis of Amide **13**



With a short and stereoselective route to spirocyclic intermediate **13** secured, we addressed its hydrolysis before studies on the key Beckmann rearrangement were launched. To our surprise, amide **13** proved to be extremely resistant to hydrolytic cleavage either under acidic or basic conditions. Different protocols were tried (LiOH, THF/H_2O/MeOH (3:1:1);[8] LiOH, THF, H_2O, H_2O_2[9]) but no reaction was observed even after heating a dioxane solution of amide **13** with concd sulfuric acid for 18 h or with 5 M ethanolic NaOH for 8 h. Under the latter condition, partial epimerization at C-14 was observed. Intrigued by the lack of reactivity of amide **13**, we decided to examine its ground-state conformation by ab initio calculations [B3LYP/6-31g(d,p)].[10] A conformation search suggested conformations A−C as the three most populated states of amide **13** (Scheme 3) with conformation B 8.0 kcal·mol^{-1} more stable then the other two conformers. This result is also supported by the ^{1}H NMR coupling constant between H13 and H14 (J = 10.6 Hz) in good agreement with the antiperiplanar arrangement observed for these hydrogens in the optimized geometry of conformer B.

Scheme 3. Ground-State Conformations of Amide **13**



The origin of this conformation bias seems to be a favored electronic interaction involving the HOMO of the amide carbonyl and the LUMO of ketone in **13**. Nucleophilic attack at the amide carbonyl in its most populated conformation B would be precluded by the ketone carbonyl blocking the amide carbonyl *Re* face and by the orthogonal methyl group at C-14 hindering its *Si* face.

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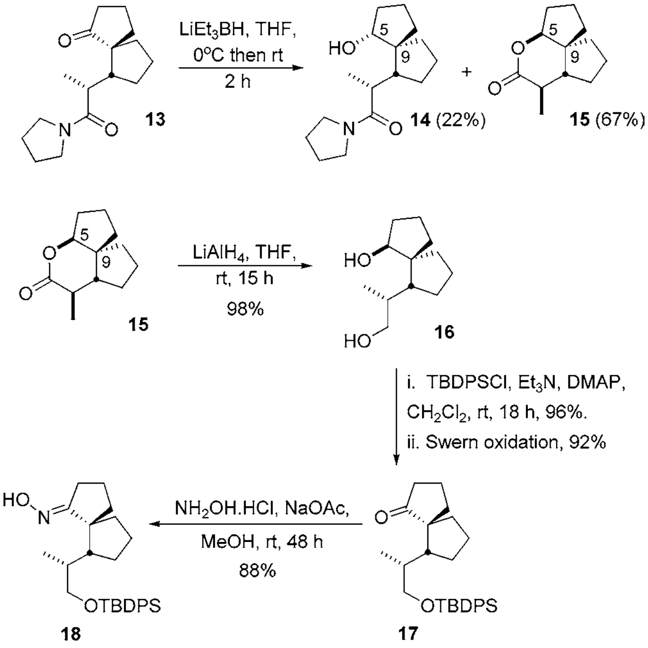
We then reasoned that the requisite amide cleavage might be better carried out via intramolecular assistance by a temporary hydroxyl group installed at C-5 following ketone reduction (Scheme 4). In the event, the planned transformation was carried out with $LiEt_3BH$ to afford lactone **15** (67% yield) together with its C5-epimeric alcohol **14** (22% yield).[11] After working out a way to cleave the recalcitrant amide bond, we straightforwardly converted lactone **15** to the corresponding bicyclic ketone **17** (86% yield, three steps) and the latter to oxime **18** (88% yield).

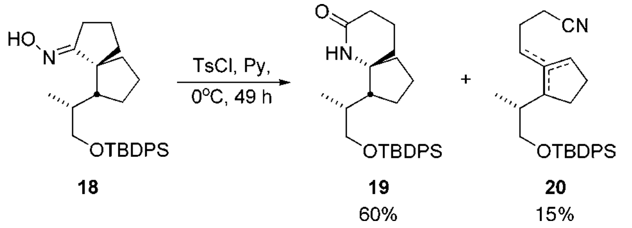
Scheme 4. Synthesis of Oxime **18**



Our initial attempts to carry out the Beckmann rearrangement with oxime **18** were plagued by either incomplete conversion (TsCl, NaOH, acetone/H_2O, reflux 4 h) or by extensive formation of a mixture of olefins **20** which arise by a competitive fragmentation process (TsCl, Py, PhH, rt, 44 h; TsCl, Py, DMAP, rt, 24 h). Although known products of the Beckmann rearrangement,[12] the formation of the fragmentation products from spirobicyclic oximes analogous to **18** is dependent on the electronic and stereoelectronic properties of the substrate and on the reaction conditions, as illustrated by the work from Corey and co-workers[13] and Ibuka and co-workers.[14]

In our hands, the key Beckmann rearrangement was best carried out when oxime **18** was treated with TsCl in pyridine as solvent at 0 °C. Under these experimental conditions, spirobicyclic lactam **19** could be isolated in 60% yield, together with 15% yield of a mixture of nitriles **20**, resulting from a competitive fragmentation process (Scheme 5).

Scheme 5. Beckmann Rearrangement of Oxime **18**



In summary, the preparation of spirobicyclic lactam **19**, possessing the common azaspirodecane moiety present in halichlorine (**1**) and structurally related alkaloids, has been accomplished in 10 steps and 13% overall yield from commercially available 1-carbomethoxycyclopentene (**9**). As the feasibility of the asymmetric version of the Michael addition/enolate alkylation has also been demonstrated by Heathcock and co-workers,[15] the route described above is also amenable to the preparation of **19** in enantiomerically pure form.

Acknowledgment. Financial support from FAPESP and CNPq is gratefully acknowleged. We also thank Mr. Angelo H. L. Machado for carrying out ab initio calculations.

Supporting Information Available: Experimental procedures and spectroscopic data for **7**, **13**, **15**, **16**, silyl ether from **16**, **17**, **18**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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