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# Total Synthesis of a Marine Alkaloid from the Tunicate *Dendrodoa grossularia*

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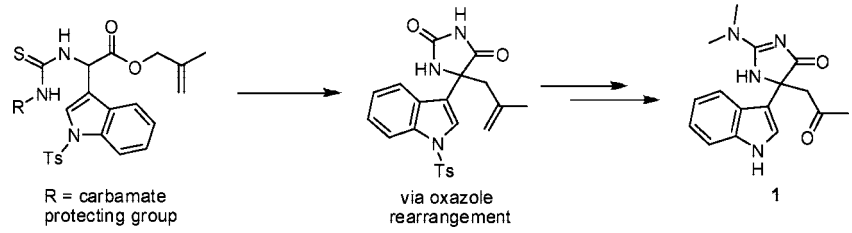
## ABSTRACT




**A short synthesis of an indole marine alkaloid (1) from the tunicate *Dendrodoa grossularia* is described. The key step in the synthesis involves a novel twist on an underutilized oxazole rearrangement, which produces the quaternary stereocenter in the molecule.**

Marine organisms have been a large source of synthetically interesting and pharmacologically important natural products.[1−4] Furthermore, the synthetic challenge of many natural products often attracts the curious organic chemist. Even some of the smaller marine natural products hold some intriguing structural scaffolds as well as hidden utility.[5]

The tunicate *Dendrodoa grossularia*, a red marine organism that grows along the coasts of Brittany and in the Baltic and North Seas, contains small heterocyclic alkaloids with unique scaffolds.[6−11] Biological studies on indole alkaloids from this tunicate displayed moderate cytotoxicity toward the L1210 leukemia cell line (4−10 $\mu$g/mL) and up to 10 ng/mL for the MCF7 and WiDr cell lines.[11,12] The latest compound (**1**) to come from this tunicate was isolated in 1998 and to the best of our knowledge has not been synthesized to date.[13]

As a continuation of our laboratory's focus on the development of new heterocyclic methodologies for the syntheses of pharmacologically significant scaffolds,[14] we report the racemic total synthesis of indole alkaloid **1**.[15] The key step in forming the quaternary stereocenter in the alkaloid utilizes a novel oxazole rearrangement[16,17] producing an oxazolone intermediate, ultimately leading to a quaternary hydantoin.

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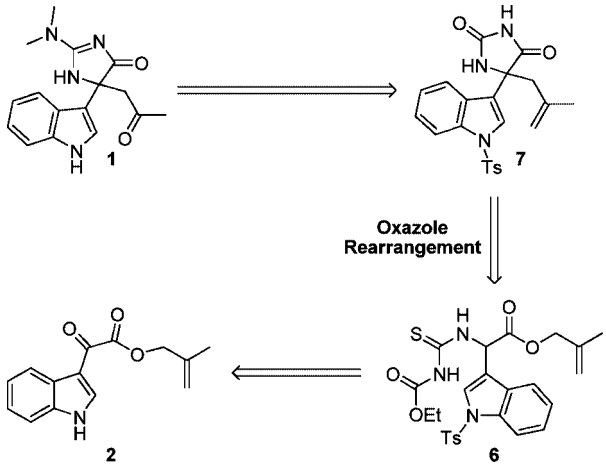
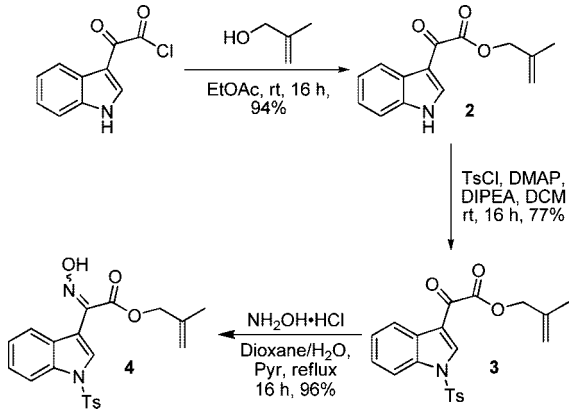
**Scheme 1.** Retrosynthesis of Indole Alkaloid (**1**)




Scheme 1 illustrates our retrosynthetic strategy for the total synthesis of indole alkaloid **1**. It was envisioned that the imidazolone moiety of the natural product could be accessed from the hydantoin intermediate **7**. Through an underutilized oxazole rearrangement, first described by Steglich and coworkers,[16,17] hydantoin **7** was thought to be formed from thiourea **6**. In turn, thiourea **6** could be obtained from keto allyl ester **2** after a few functional group manipulations.

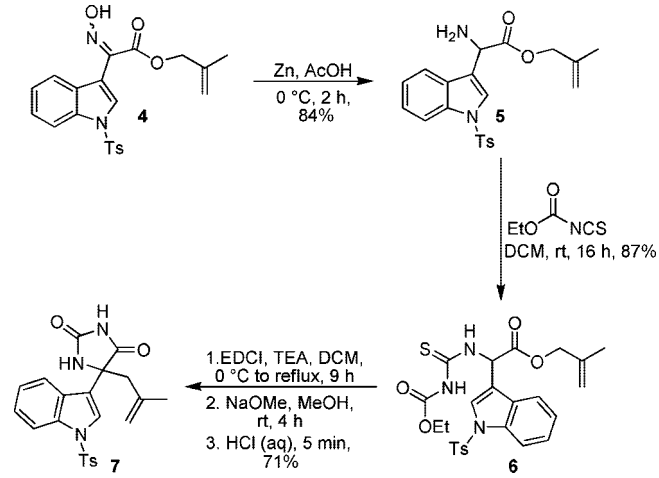
**Scheme 2.** Synthesis of Alkaloid (**1**): Formation of Oxime (**4**)




Keto allyl ester **2** (Scheme 2) was synthesized through an esterification of 2-(1*H*-indol-3-yl)-2-oxoacetyl chloride with 2-methyl-2-propen-1-ol, which is the product of a known reaction between indole and oxalyl chloride.[18] Subsequent protection of the indolic nitrogen with *p*-toluene sulfonyl chloride gave keto ester **3**, which when treated with hydroxylamine and pyridine in dioxane produced oxime **4** in 96% yield as a mixture of *E* and *Z* isomers.

Reduction of oxime **4** using zinc and acetic acid led to amine **5** (Scheme 3), which was treated with commercially

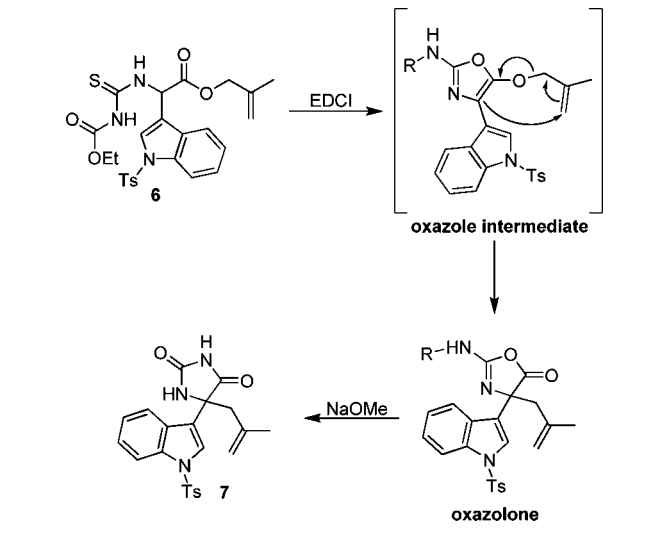
**Scheme 3.** Synthesis of Akaloid (**1**): Formation of Hydantoin (**7**)




available ethoxy carbonyl isothiocyanate to yield thiourea **6**. Subsequent treatment of thiourea **6** with EDCI followed by sodium methoxide yielded hydantoin **7** in 71% yield, resulting from an oxazole rearrangement.

The proposed mechanism for the formation of hydantoin **7** is highlighted in Scheme 4. Initially, the thiourea moiety

**Scheme 4.** Proposed Mechanism for Novel Rearrangement




was likely converted into a carbodiimide intermediate using EDCI.[19−21] Subsequently, a 5-*exo-dig* cyclization occurred

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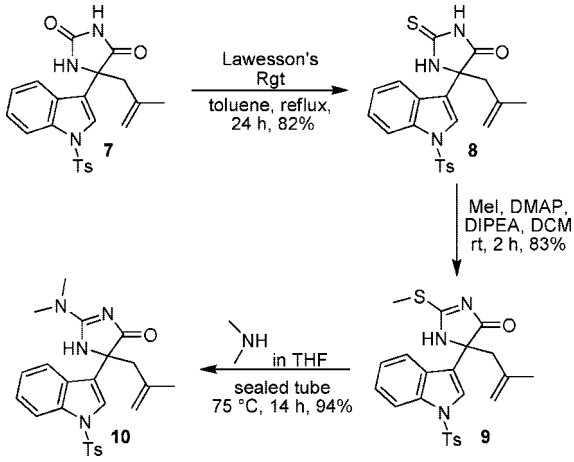
between the carbonyl oxygen of the ester and the carbodiimide to form a transient oxazole intermediate. Through a Claisen-type rearrangement, the oxazole was transformed into a quaternary oxazolone intermediate. Upon completion of the rearrangement, as indicated by TLC, a solution of sodium methoxide in methanol was added to complete the transformation from the oxazolone to hydantoin **7**.[22]

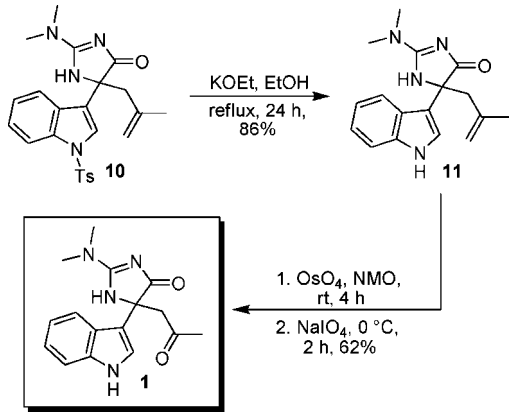
Treatment of hydantoin **7** with Lawesson's reagent[23] produced thiohydantoin **8** (Scheme 5), which was selectively

**Scheme 5.** Synthesis of Alkaloid (**1**): Formation of Imidazolone (**10**)




methylated at the thiocarbonyl using methyl iodide, DMAP, and diisopropylethylamine to furnish imidazolone **9**. After heating imidazolone **9** with dimethylamine in a sealed tube, imidazolone **10** was produced in 94% yield.

**Scheme 6.** Synthesis of Indole Alkaloid (**1**)




The final steps for the total synthesis of **1** (Scheme 6) began with the deprotection of the indole nitrogen using potassium ethoxide and ethanol under refluxing conditions to produce imidazolone **11** in 86 % yield. Finally, oxidation of the terminal alkene was achieved through a two-step/one-pot modified Johnson−Lemieux[24] reaction to give indole alkaloid **1**,[25] whose crystal structure is shown in Figure 1.

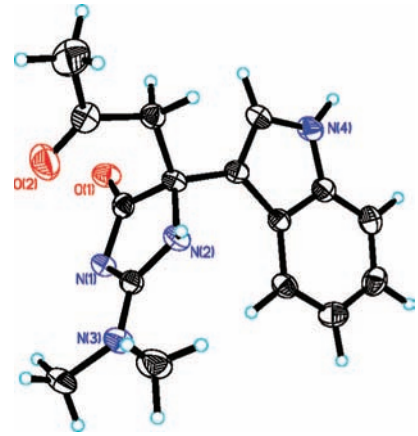



**Figure 1.** X-ray crystal structure of indole alkaloid **1**.

In short, we reported a concise total synthesis of a new indole alkaloid from the tunicate *Dendrodoa grossularia*. The key step utilized a new twist on a rarely used oxazole rearrangement to afford the quaternary stereocenter in the molecule.

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**Supporting Information Available:** Experimental procedures and characterizations for all new compounds (**1**−**11**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The final product is spectroscopically identical to the isolated natural product. See Supporting Information for a tabulated comparison of spectra.