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# Synthesis of cleavamine-type indole alkaloids and their 5-nor derivatives by a ring-closing metathesis–vinyl halide Heck cyclization strategy

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ABSTRACT

An indole-templated RCM has been used to assemble the central medium-sized rings of the indole *upper-half* of vinorelbine and the cleavamine-type alkaloids. From these key intermediates, the bridged tetracyclic framework of the alkaloids is completed with the insertion of a 2-ethylpropeno unit, by N-alkylation followed by a challenging *endocyclic* vinyl halide Heck cyclization. The usefulness of the approach is illustrated with the synthesis of (±)-cleavamine and (±)-dihydrocleavamine.



## 1. Introduction

The remarkable structural diversity of indole alkaloids as well as their significant biological activities have long caught the attention of synthetic organic chemists, providing inspiration for the development of novel synthetic strategies. Our longstanding interest in this area led us to envisage a combination of two well-established C–C bond-forming reactions, a ring-closing metathesis (RCM),[1] and a Heck cyclization,[2] for the rapid assembly of the bridged tetracyclic topography of some indole alkaloids. Based on this strategy, we have recently developed a unique approach to the alkaloids ervitsine[3] and apparicine.[4] In particular, we have shown that after an indole-templated RCM to build the central medium-sized ring of these alkaloids, a vinyl halide Heck coupling accomplishes the closure of the piperidine ring with the concomitant placement of the exocyclic 20*E*-ethylidene substituent (Fig. 1). Other authors have also made use of similar *exocyclic* vinyl halide Heck couplings for the assembly of the bridged core of indole alkaloids including pentacyclic *Strychnos* alkaloids,[5] strychnine,[6] and minfiensine.[7]

As an extension of our earlier work, we considered applying the RCM–Heck double annulation strategy for the construction of other bridged indolic structures, such as those included in cleavamines and their 5-nor derivatives (Fig. 2). The cleavamine-type alkaloids

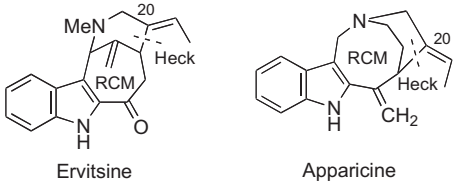


**Fig. 1.** Previous applications of the RCM–Heck cyclization strategy.

(cleavamine, velbanamine, or (+)-20*R*-dihydrocleavamine) are a small subgroup of tetracyclic natural bases belonging to the *Iboga* family[8] that are structurally characterized by a central nine-membered ring and a bridged 3-substituted piperidine moiety, featuring a 1-azabicyclo[6.3.1]dodecane framework. The same tetracyclic skeleton is also found in the *Aspidosperma* alkaloid quebrachamine. Cleavamines are of particular interest not only because they have provided key synthetic intermediates for pentacyclic *Iboga* derivatives[9] but also because they constitute the indole *upper-half* of the well known antimitotic bisindole *Catharanthus* alkaloids vinblastine and vincristine.[10] On the other hand, the 5-nor tetracyclic architecture, featuring a 1-azabicyclo[5.3.1]undecane bridged system, constitutes the indole *upper-half* of the semisynthetic derivative vinorelbine (5′-noranhydrovinblastine), also used in cancer chemotherapy.[10,11]

As depicted in Scheme 1, our synthetic plan for the assembly of the bridged arrangements of the above alkaloids (**I**) commenced

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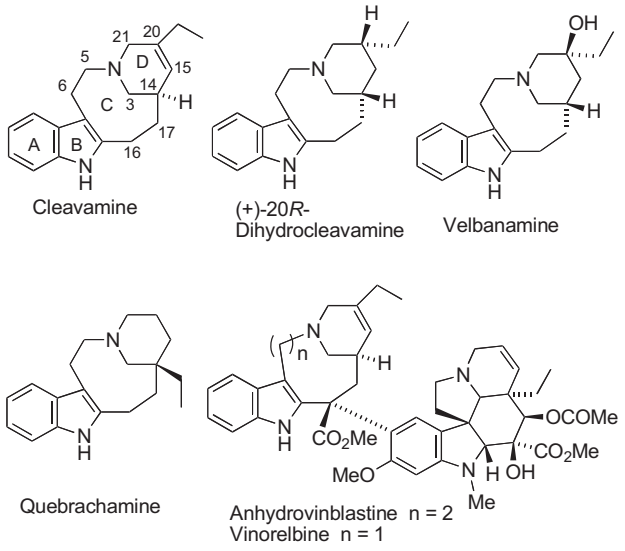
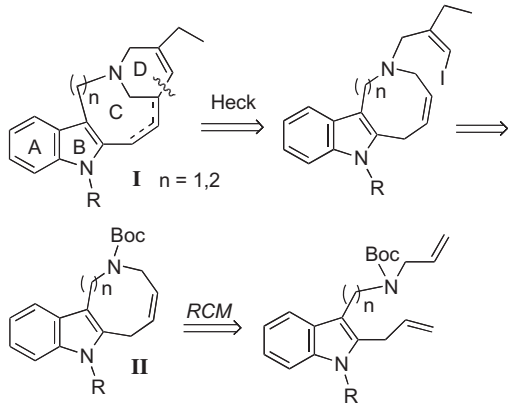



**Fig. 2.** Cleavamine, *Catharanthus*, and related alkaloids.




**Scheme 1.** Synthetic strategy.

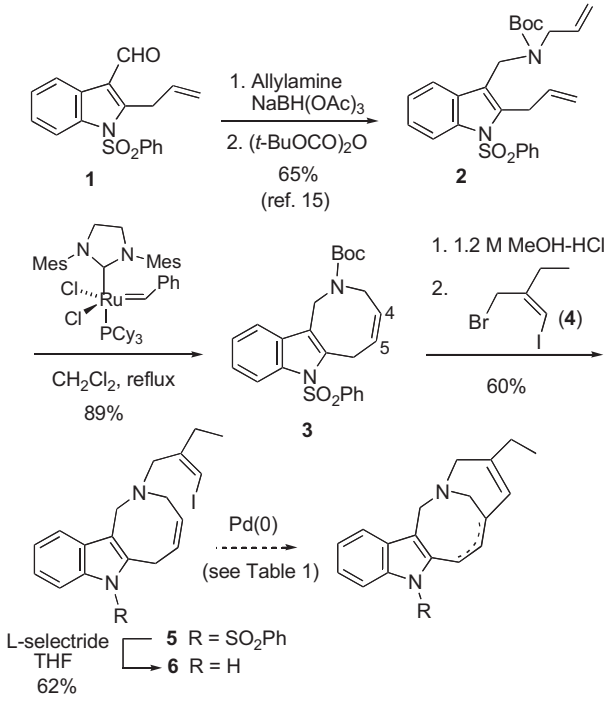
with the metathetic closure of appropriate 2,3-dialkenyl indoles to provide the tricyclic ABC substructures **II**, containing a central eight- or nine-membered ring.[12] From these pivotal intermediates, the carbon skeleton would be completed with the insertion of a 2-ethylpropeno unit by N-alkylation followed by a challenging *endocyclic* vinyl halide Heck cyclization upon the double bond left by the RCM step. It should be noted that, apart from our own work on the synthesis of apparicine,[4] Heck cyclizations upon cyclooctenes or cyclononenes to produce strained bridged systems are rare, most reported examples dealing with cyclizations from more robust aryl halides.[13]

This article describes the development of the above annulation chemistry for the assembly of the 5-nor cleavamine skeleton and the formulation of a novel synthetic approach to the alkaloids cleavamine and dihydrocleavamine.[14]

## 2. Results and discussion

### 2.1. Heck cyclization upon azocino[4,3-*b*]indoles: access to 5-nor cleavamines

We set out to study the construction of the 1-azabicyclo[5.3.1]undecane bridged system (**I**, $n$=1, Scheme 1), which defines the indole *upper-half* of vinorelbine, targeting azocino[4,3-*b*]indole **3** (Scheme 2), with the 4,5-double bond functionality required for the subsequent Heck coupling. This compound was easily prepared applying a slight modification of our previously reported procedure.[15] Thus, reductive amination of aldehyde **1** with allylamine followed by protection of the resulting secondary amine with a Boc group gave carbamate **2**, which smoothly underwent RCM in the presence of the second-generation Grubbs catalysts to give **3** in 58% overall yield. At this point, access to the more advanced synthetic intermediate **5** required the manipulation of the aliphatic nitrogen to install the haloalkenyl chain. The *N*-Boc group was successfully removed using a mild acid protocol (1.2 M HCl in MeOH at rt) and the resulting secondary amine was directly alkylated with allylic bromide **4**[16] to give **5** in 60% overall yield. We also considered of interest to prepare the respective indole-deprotected substrate **6**, which was accomplished by treatment of **5** with L-Selectride in refluxing THF (62% yield). This reductive protocol was chosen to minimize both the previsible isomerization of the double bond to its indole-conjugated counterpart[4] and the previsible elimination of the haloalkenyl chain under the standard basic conditions.




**Scheme 2.** Access to the 1-azabicyclo[5.3.1]undecane bridged system.

A detailed investigation into the Heck reaction was then undertaken using vinyl iodide **5** as the main substrate (Table 1). We first examined the reaction under a cationic protocol ($Pd(OAc)_2$, $PPh_3$, $Ag_2CO_3$, entry 1) similar to that successfully applied in our synthesis of apparicine,[4] but only the unchanged material was recovered using either refluxing toluene or acetonitrile as solvent. Without the additive $Ag_2CO_3$, the inclusion of proton-sponge® as base led to minor amounts of tetracycle **7**, coming from the expected *exo* cyclization with the generation of a disubstituted indole-conjugated double bond (entry 2). More satisfactorily, the yield of **7** increased to 40% using $Pd(PPh_3)_4$ as the palladium catalyst (entry 3). In both cases, minor amounts of another cyclized product, not stable enough to be characterized, were detected in the reaction mixtures.

The application of the latter conditions to the *N*-unsubstituted indolic substrate **6** resulted in a cleaner cyclization, producing tetracycle **8** as the only product in 45% yield (entry 4). This compound could be alternatively obtained by removal of the *N*-phenylsulfonyl group of tetracycle **7** under standard basic conditions (67%,