ORGANIC LETTERS

2011
Vol. 13, No. 8
2042–2045

A Straightforward Synthetic Entry to Cleavamine-Type Indole Alkaloids by a Ring-Closing Metathesis−Vinyl Halide Heck Cyclization Strategy

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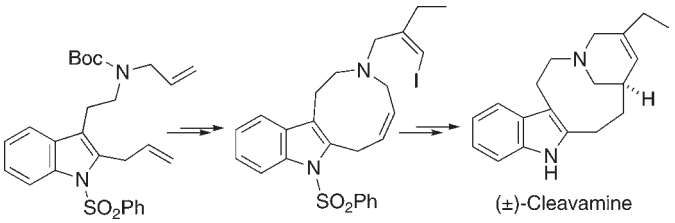
Received February 17, 2011

ABSTRACT



An indole-templated ring-closing metathesis has been used to create the central nine-membered ring of the cleavamine-type alkaloids. A subsequent intramolecular vinyl halide Heck reaction upon the resulting azacyclononene ring completes the assembly of the strained 1-azabicyclo[6.3.1]dodecane framework of the alkaloids. The usefulness of the approach is illustrated with the synthesis of (±)-cleavamine and (±)-dihydrocleavamine.

Indole alkaloids belonging to the *Iboga* family have long caught the attention of synthetic organic chemists owing to their complex architecture as well as their diverse and important biological activities.[1] Most of these alkaloids (*e.g.*, catharanthine, Figure 1) are structurally characterized by a pentacyclic skeleton with indole and isoquinuclidine rings fused by a seven-membered C ring. However, there is a small subgroup of natural bases (cleavamine, velbanamine, or (+)-20*R*-dihydrocleavamine) that exhibit a 16,21-*seco* structure, featuring a bridged 1-azabicyclo-[6.3.1]dodecane framework. The cleavamine alkaloids are of particular interest not only because they have provided key synthetic intermediates for pentacyclic *Iboga* derivatives[2] but also because they constitute the indole *upper half* of the antitumoral bisindole *Catharanthus* alkaloids vinblastine and vincristine.[3]

Our long-standing interest in the synthesis of indole alkaloids led us to envisage a straightforward synthetic approach to the bridged cleavamine framework, relying on an indole-templated ring-closing metathesis (RCM)[4] to construct the central nine-membered ring and a vinyl halide Heck cyclization[5] to close the piperidine ring.

As shown in Scheme 1, the metathetic ring closure of a 2,3-dialkenylindole would provide a tricyclic ABC substructure (i.e., azonino[5,4-*b*]indole **I**), from which the carbon skeleton would be completed by inserting a 2-ethylpropene unit between the aliphatic nitrogen and C-5. Thus, after *N*-alkylation with the appropriate haloalkenyl halide, an intramolecular Heck coupling upon the 2-allylindole moiety would serve to close the piperidine ring and at the same time install the requisite 20-ethyl group. This Letter describes the development of the above annulation chemistry and its use in the total

(1) For reviews, see:(a) Cordell, G. A. In *Indoles, The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: New York, 1983; Vol. 25, Part 4, Chapter 10. (b) Saxton, J. E. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley: Chichester, 1994; Supplement to Vol. 25, Part 4, Chapter 10.

(2) Sundberg, R. J.; Smith, S. Q. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Presss: Amsterdam, 2002; Vol. 59, Chapter 2.

(3) Brossi, A.; Suffness, M., Eds. *The Alkaloids*, Vol. 37; Academic Press: San Diego, 1990.

(4) For general reviews, see: (a) Grubbs, R. H., Ed. *Handbook of Metathesis*; Wiley-VCH: Weinheim, 2003; Vol. 2. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.

(5) For general reviews, see: (a) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-WCH: New York, 2004; pp 217−316. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680.

10.1021/ol200437k
Published on Web 03/10/2011

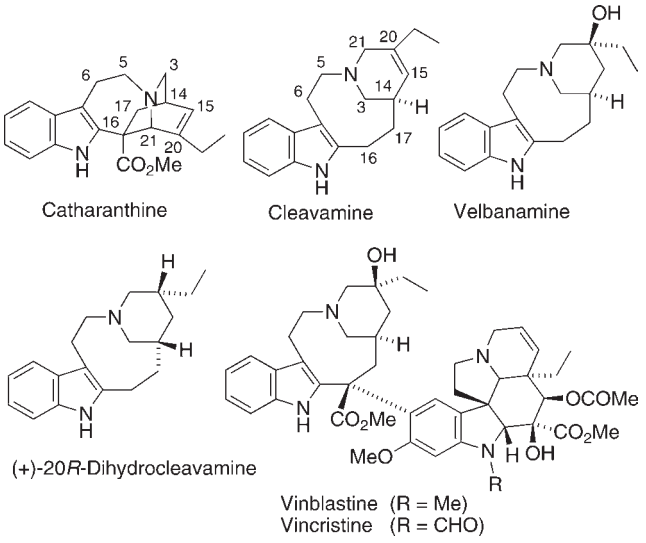
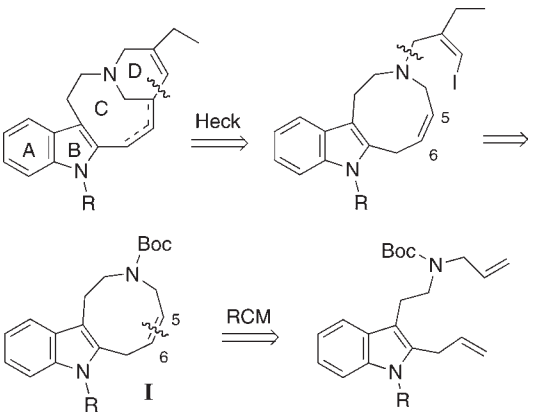


Figure 1. *Iboga* and *Catharanthus* indole alkaloids.

synthesis of (±)-cleavamine and its 14,20-*cis*-dihydro derivative.

Although the RCM methodology has become a powerful tool for the synthesis of medium sized rings,[6] the construction of nine-membered rings can be challenging.[7] Based on our previous RCM synthesis of azocinoindoles,[8] we assumed that both the fused indole ring and the nitrogen carbamate would operate synergistically, thus favoring the ring closure. On the other hand, although Heck couplings of vinyl halides and elaborated cyclohexenes[9] or cycloheptenes[10] have proved to be useful for the assembly of the bridged core of several indole alkaloids, cyclizations upon higher cycloalkenes to produce strained bridged systems similar to our proposal are

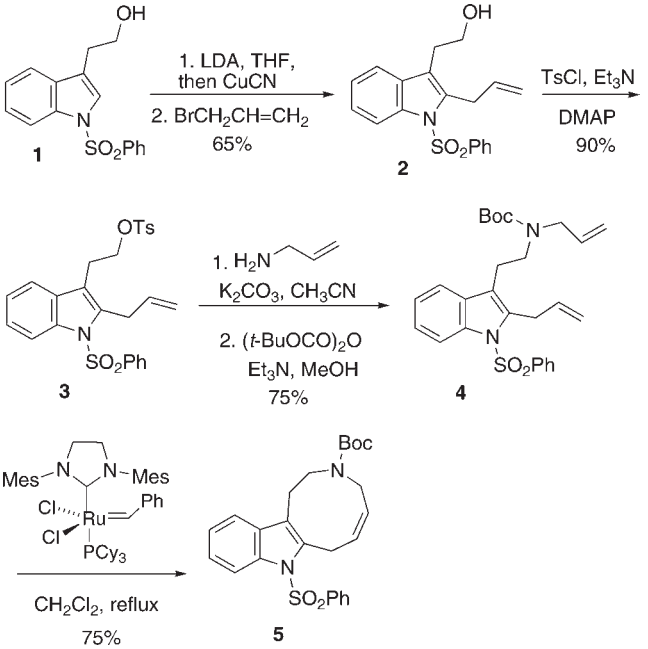
Scheme 1. Synthetic Strategy



rare.[11] In this context, we have recently become involved in vinyl halide Heck reactions upon azocine rings for the total synthesis of apparicine.[12]

We set out to study the indole-templated RCM en route to cleavamine, targeting azonino[5,4-*b*]indoles **I**, with the 5,6 double bond functionality required for the Heck coupling. To this end, indole **4** (Scheme 2), which is equipped with a Boc group at the aliphatic nitrogen and a robust phenylsulfonyl at the indole nitrogen, was selected as the starting diene. This compound was efficiently prepared from the protected tryptophol **1**[13] by successive introduction of the required alkenyl appendages. Thus, the exposure of **1** to excess LDA and CuCN followed by the reaction of the intermediate organocopper with allyl bromide led to 2-allylindole **2** (65%), which was uneventfully converted

Scheme 2. Synthesis and RCM of Diene **4**



(6) (a) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963–3007. (c) Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5740–5750.

(7) For instance, see: (a) Clark, J. S.; Marlin, F.; Nay, B.; Wilson, C. *Org. Lett.* **2003**, *5*, 89–92. (b) Enders, D.; Lenzen, A.; Backes, M.; Janeck, C.; Catlin, K.; Lannou, M.-I.; Runsink, J.; Raabe, G. *J. Org. Chem.* **2005**, *70*, 10538–10551. (c) Schwartz, K. D.; White, J. D. *Org. Lett.* **2011**, *13*, 248–251.

(8) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Tetrahedron* **2007**, *63*, 861–866.

(9) (a) Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695–1698. (b) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030–3031. (c) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685–2686. (d) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem.—Eur. J.* **2000**, *6*, 655–665. (e) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **2001**, *123*, 9324–9337. (f) Mori, M.; Nakanishi, M.; Kahishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801–9807. (g) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368–5377. (h) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472–3473.

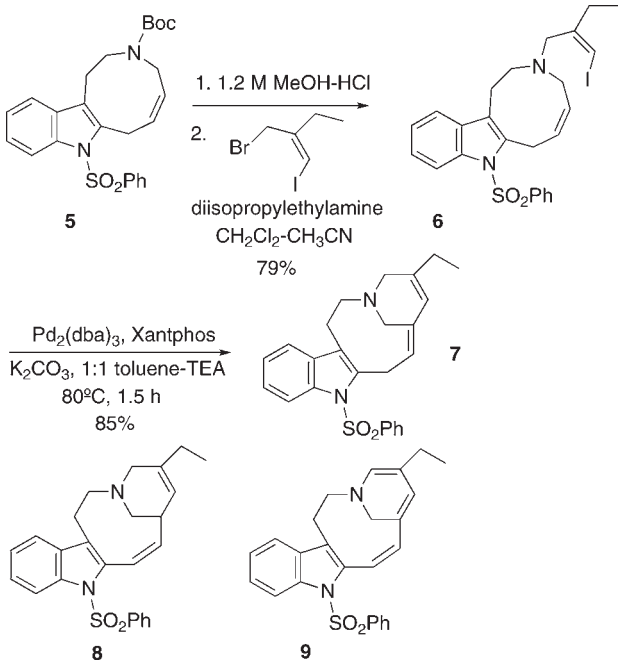
(10) (a) Birman, V. B.; Rawal, V. H. *J. Org. Chem.* **1998**, *63*, 9146–9147. (b) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Synlett* **2008**, 667–670.

(11) For related Heck processes involving more robust aryl halides, see: (a) Grigg, R.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1998**, *39*, 4139–4142. (b) Ribelin, T. P.; Judd, A. S.; Akritopoulou-Zanze, I.; Henry, R. F.; Cross, J. L.; Whittern, D. N.; Djuric, S. W. *Org. Lett.* **2007**, *9*, 5119–5122. (c) See also ref 7b.

into diene **4** by alkylation of the corresponding tosylate **3** with allylamine and subsequent protection of the resulting secondary amine (75% for the two steps). As anticipated, ring closure of diene **4** proceeded in the presence of the second-generation Grubbs catalyst in refluxing CH_2Cl_2. Satisfactorily, the reaction was completed in 2 h 30 min and azoninoindole **5**, with the *Z* configuration of the double bond, was isolated in 75% yield.

At this point, access to the more advanced synthetic intermediate **6** required the manipulation of the aliphatic nitrogen of **5** to install the haloalkenyl chain for the subsequent Heck reaction. 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 (*Z*)-3-bromo-2-ethyl-1-iodopropene[14] to give **6** in a 79% overall yield (Scheme 3).

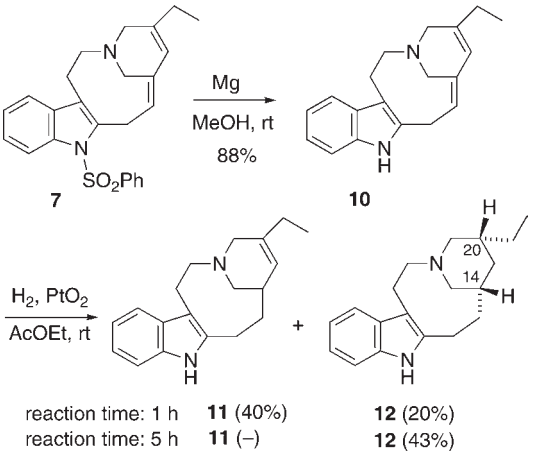
Scheme 3. Assembly of the 1-Azabicyclo[6.3.1]dodecane Framework by Heck Cyclization



The stage was now set for the assembly of the cleavamine skeleton by intramolecular coupling of the vinyl iodide and the double bond included in the azonine ring. We expected tetracycle **8** to be preferentially formed after an *exo* cyclization with generation of a disubstituted, indole-conjugated double bond. Our first assays were discouraging since under a variety of conditions, including palladium precatalysts [$Pd(PPh_3)_4$, Pd_2dba_3], ligands (BINAP, dppe), and additives (proton-sponge, Et_3N, diisopropylethylamine) in refluxing toluene, we obtained mixtures of the starting material and variable amounts of tetracycle **9**, which presumably arose from **8** by oxidation. Although we were able to isolate **8** when using shorter reaction times or lower temperatures, it proved to be highly unstable, slowly being converted into **9** under extractive workup or column chromatography.[15] Fortunately, after screening other conditions for the Heck reaction, we found that the outcome of the cyclization changed completely on exposure of vinyl iodide **6** to Pd_2dba_3/xantphos and K_2CO_3 in toluene−Et_3N at 80 °C within a short reaction time (1.5 h). Tetracycle **7**, embodying a trisubstituted bridgehead double bond, was isolated in a yield as high as 85%. In contrast to its regioisomer **8**, tetracycle **7** showed no tendency to undergo oxidation. Its two-vinylic proton structure was clearly confirmed by a combination of bidimensional NMR techniques ($^1H-^1H$ COSY, HSQC, and HMBC).

With the 1-azabicyclo[6.3.1]dodecane framework in hand, the synthesis of (±)-cleavamine only required the deprotection of the indole nitrogen and the selective reduction of the bridgehead double bond. Thus, reductive removal (Mg, MeOH, rt) of the phenylsulfonyl group of **7** led to **10**, which was subjected to catalytic hydrogenation in AcOEt (Scheme 4). Gratifyingly, (±)-cleavamine **11** could be isolated as the major product (40% yield) after a short reaction time (1 h), although minor amounts of 14,20-*cis*-dihydrocleavamine **12** were also formed. As expected, longer reaction times (5 h) gave **12** as the only product (43%). Synthetic cleavamines displayed ^1H and ^{13}C NMR spectral data identical to those reported for the natural products.[16,17]

Scheme 4. Completion of the Synthesis of Cleavamines



In conclusion, we have developed a concise entry to the bridged tetracyclic core of cleavamine alkaloids via a

(12) (a) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Chem. Commun*. **2009**, 3372–3374. (b) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Roca, T.; García-Díaz, D.; Alonso, S. *J. Org. Chem*. **2009**, *74*, 8359–8368.

(13) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Leahy, E. M.; Salvino, J.; Arison, B.; Cichy, M. A.; Spoors, P. G.; Shakespeare, W. C.; Sprengeler, P. A.; Hamley, P.; Smith, A. B., III; Reisine, T.; Raynor, K.; Maechler, L.; Donaldson, C.; Vale, W.; Freidinger, R. M.; Cascieri, M. R.; Strader, C. D. *J. Am. Chem. Soc*. **1993**, *115*, 12550–12568.

(14) Zhang, Y.; Herndon, J. W. *Org. Lett*. **2003**, *5*, 2043–2045.

(15) The structure of **8** could be determined by ^1H NMR analysis of its corresponding hydrochloride (see Supporting Information for details).

sequence that features an indole-templated RCM to build their tricyclic ABC substructure and a challenging vinyl halide Heck cyclization to finally assemble the bridged skeleton. This double annulation strategy has been applied to the total synthesis of (±)-cleavamine and its 14,20-*cis*-dihydro derivative, which requires a total of 10 steps from tryptophol **1** and proceeds via eight isolated intermediates. The application of the strategy to the synthesis of other alkaloids embodying indolo-fused bridged systems is in progress in our laboratory.

Acknowledgment. We thank the Ministerio de Ciencia e Innovación, Spain, for financial support (Project CTQ2009-07175) and the University of Barcelona for a grant to S.A.

Supporting Information Available. Experimental details and copies of ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) For NMR data of cleavamine, see: (a) Kutney, J. P.; Brown, R.; Piers, E. *Can. J. Chem.* **1965**, *43*, 1545–1552. (b) Imanishi, T.; Nakai, A.; Yagi, N.; Hanaoka, M. *Chem. Pharm. Bull.* **1981**, *29*, 901–903. (c) Wenkert, E.; Hagaman, E. W.; Kunesch, N.; Wang, N.-Y. *Helv. Chim. Acta* **1976**, *59*, 2711–2723.

(17) For NMR data of (+)-20*R*-dihydrocleavamine, see: van Beek, T. A.; Verpoorte, R.; Svendsen, A. B. *Tetrahedron* **1984**, *40*, 737–748.