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Tandem Metathesis Reactions of Oxabicyclo[2.2.1]heptenes: Studies on the Spirocyclic Core of Cyclopamine

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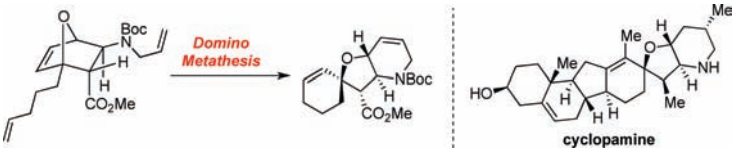
ABSTRACT



A rapid approach to the spirocyclic core of cyclopamine was achieved in four steps from 2-pentenyl-furan. A furan Diels–Alder reaction followed by a one-pot dehalogenation/amination sequence provides the oxabicyclic triene that upon treatment with Grubbs' catalyst undergoes smooth rearrangement to the tricyclic core.

Natural products have long served as new sources of diverse therapeutic agents for the treatment of various cancers, often acting through previously unrecognized cellular pathways. Although these compounds often function as general cytotoxins by targeting the cell cycle machinery of fast growing cells, there are also naturally occurring compounds that target some of the underlying mechanisms responsible for cell dysregulation.[1] One such natural agent that has attracted considerable interest is the steroidal alkaloid cyclopamine (Figure 1).

This unusual and complex plant-derived steroid has been known for over 50 years and was originally isolated owing to its severe teratogenic effects, inducing cyclopia in the offspring of pregnant sheep that grazed on corn lilies (*Veratrum californicum*).[2] It would not be until 1998 that the cellular target of cyclopamine was identified as the hedgehog pathway.[3] The hedgehog (Hh) signaling pathway is active in the development of multiple tissue types during the embryonic stage and can become reactivated during tissue repair and in certain malignancies.[4] Secreted Hh protein binds the twelve transmembrane protein patched (Ptch) which, in turn, relieves the inhibition of the seven transmembrane protein smoothened (Smo). This allows Smo to transduce the signal to the nucleus and activate the downstream targets, through the Gli family of transcription factors, which regulate numerous gene products involved in tissue growth and differentiation. Cyclopamine was shown to bind directly to Smo and antagonize Gli activation by Hh and produce strong antiproliferative effects.[5]

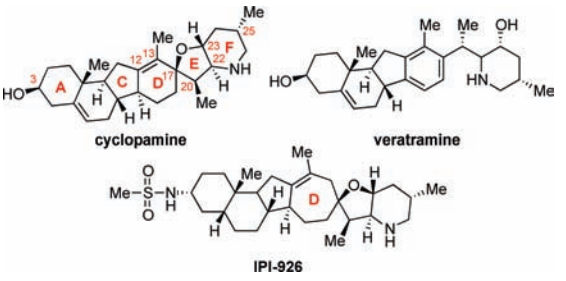


Figure 1. Structure of cyclopamine, veratramine, and IPI-926.

(1) Sarkar, F. H.; Lia, Y.; Wanga, Z.; Konga, D. *Cell. Signal* **2009**, *21*, 1541.

(2) (a) Keeler, R. F.; Binns, W. *Proc. Soc. Exp. Biol. Med.* **1964**, *116*, 123. (b) Keeler, R. F.; Binns, W. *Teratology* **1968**, *1*, 5. (c) Keeler, R. F. *J. Agric. Food. Chem.* **1969**, *17*, 473.

(3) Cooper, M. K.; Porter, J. A.; Young, K. E.; Beachy, P. A. *Science* **1998**, *280*, 1603.

(4) Scales, S. J.; de Sauvage, F. J. *Trends Pharmacol. Sci.* **2009**, *30*, 303.

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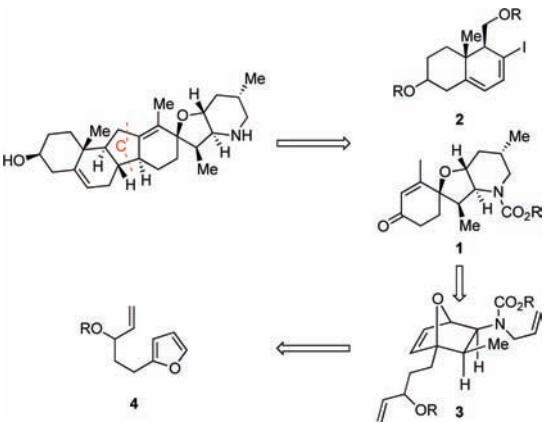
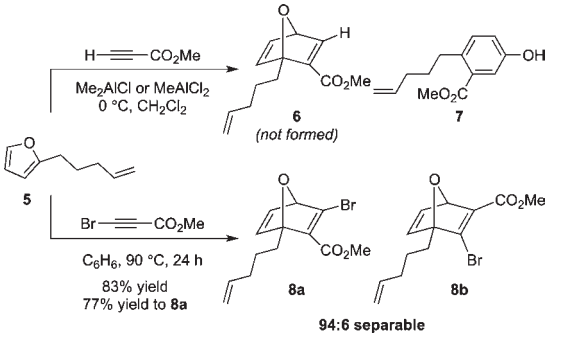
The direct application of cyclopamine has been complicated by some of the features of this complex natural product including poor aqueous solubility and instability in acid, whereby cyclopamine undergoes a dehydrative aromatization to give the inactive veratramine.[6] Currently, a semisynthetic analog of cyclopamine, IPI-926, with an expanded D-ring is in phase II trials for the treatment of metastatic pancreatic cancer.[7] The interesting structure and exciting biological activity of this natural product has prompted us to develop synthetic routes to the natural product and various analogs. A retrosynthesis was formulated that would rely on some key metathesis chemistry we have developed over the past several years.

Scheme 1. Retrosynthetic Analysis of Cyclopamine



This retrosynthetic analysis of cyclopamine[8] is centered upon an overall convergent pathway that anticipates a late stage union of fragments **1** and **2** with subsequent formation of the cyclopentyl C-ring. Key to this strategy is the development of a route to a suitable DEF-tricycle such as **1**. As this unit contains an integral and highly substituted tetrahydrofuran substructure, with both spiro (C17) and linear (C22/23) annulations, we were attracted to the use of a furan-based strategy to access these types of systems. We have previously shown that oxabicyclic systems containing a pendant olefin undergo efficient bond reorganization upon treatment with Grubbs' catalyst to deliver various oxaspiro systems.[9] We wished to examine an extension of this method whereby ring opening of a suitably functionalized oxabicyclo[2.2.1]heptene would be coupled to two independent ring-closing metathesis reactions. This would allow a direct conversion of a bicyclic intermediate such as **3** into the tricyclic core of these alkaloids. It was anticipated that the highly substituted oxabicyclic derivative that contains four contiguous stereogenic centers (C-17/20/22/23) could be derived easily from simple furans **4** through a Diels–Alder reaction (Scheme 1).

Scheme 2. Diels–Alder Reaction of a 2-Substituted Furan



Lithiation of furan and treatment with 1-bromopentene gave the 2-substituted furan **5** that was reacted with acetylenic dienophiles under both thermal and Lewis acid conditions. Reaction of **5** with methylpropriolate under thermal conditions (rt–90 °C, neat or 3.0 M in benzene) failed to deliver the desired adduct **6**, returning only unreacted starting materials. The addition of mixed aluminum catalysts that had been effective in some related intramolecular cycloadditions[10] resulted in a rapid conversion to the phenol **7**, likely through opening of the primary bridged adduct. Ultimately, we were pleased to find that the more deactivated 3-bromomethyl propriolate[11] underwent a high yielding and highly selective Diels–Alder reaction to give the oxabicyclo[2.2.1]heptadiene **8a** along with small amounts of the undesired regioisomer **8b** (Scheme 2). The resultant β-bromoenoate moiety derived from the alkyne offered a direct access point for installation of the C22–nitrogen side chain (Scheme 3).

Initial attempts to substitute the β-bromide with amine nucleophiles were frustrated by the propensity for rapid overaddition, likely driven by relief of ring strain upon removal of two sp^2 centers from the bridged system. To prevent this unwanted overaddition, initial reduction of the β-bromide was investigated. Exposure of **8a** to a buffered zinc–silver couple[12] produced the desired enoate

(6) Borzillo, G. V.; Lippa, B. *Curr. Top. Med. Chem.* **2005**, *5*, 147.

(7) (a) Tremblay, M. R.; Nevalainen, M.; Nair, S. J.; Porter, J. R.; Castro, A. C.; Behnke, M. L.; Yu, L. C.; Hagel, M.; White, K.; Faia, K.; Grenier, L.; Campbell, J. C.; Woodward, C. N.; Hoyt, J.; Foley, M. A.; Read, M. A.; Sydor, J. R.; Tong, J. K.; Palombella, V. J.; McGovern, K.; Adams, J. *J. Med. Chem.* **2008**, *51*, 6646. (b) Tremblay, M. R.; Lescarbeau, A.; Grogan, M. J.; Tan, E.; Lin, G.; Austad, B. C.; Yu, L. C.; Behnke, M. L.; Nair, S. J.; Hagel, M.; White, K.; Conley, J.; Manna, J. D.; Alvarez-Diez, T. M.; Hoyt, J.; Woodward, C. N.; Sydor, J. R.; Pink, M.; MacDougall, J.; Campbell, J. C.; Cushing, J.; Ferguson, J.; Curtis, M. S.; McGovern, K.; Read, M. A.; Palombella, V. J.; Adams, J.; Castro, A. C. *J. Med. Chem.* **2009**, *52*, 4400. (c) Tremblay, M. R.; Nesler, M.; Weatherhead, R.; Castro, A. C. *Expert Opin. Ther. Pat.* **2009**, *19*, 1039.

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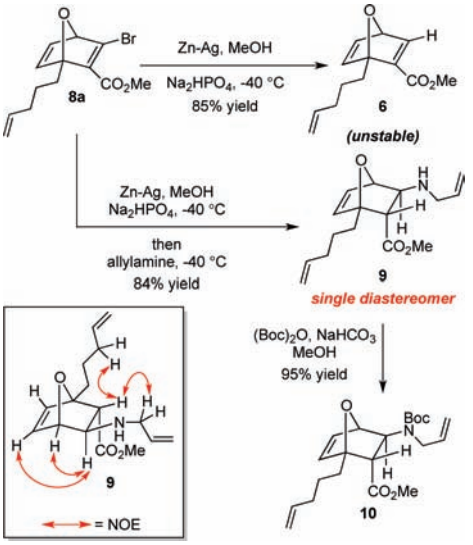
(10) Wright, D. L.; Robotham, C. V.; Aboud, K. *Tetrahedron Lett.* **2002**, *43*, 943.

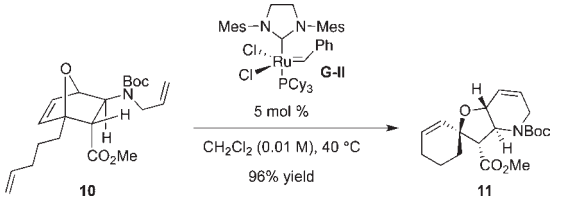
(11) (a) For a preparation, see: Leroy, J. *Org. Synth.* **1998**, *9*, 129. (b) For a similar example, see: Rainier, J. D.; Xu, Q. *Org. Lett.* **1999**, *1*, 27. Xu, Q.; Weeresakare, M.; Rainier, J. D. *Tetrahedron* **2001**, *57*, 8029.

Scheme 3. Elaboration of an Oxabicyclo[2.2.1]heptadiene



6 which was highly unstable. Fortunately, it was possible to develop a one-pot sequence that involved initial dehalogenation followed by immediate conjugate addition of allylamine to produce ester **9** as a single diastereomer as determined by NOE correlation.

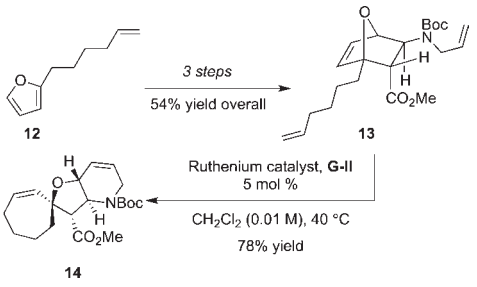
Scheme 4. A Domino Metathesis Approach to the DEF-Rings of Cyclopamine



The addition of the amine had occurred, as expected, from the *exo*-face, which establishes the correct relative stereochemical relationships between C-23 and C-17/22. This conjugate addition also sets the configuration at what would be C-20 of cyclopamine upon protonation of the intermediate enolate. Initially, it was hoped that the allylamino and pentenyl chains flanking this center would favor *endo*-protonation to position the carbomethoxy group in the *exo*-position as a direct precursor to the methyl group. However, protonation occurred exclusively from the *exo*-face, giving **9** as the only diastereomer, which will necessitate an overall inversion in the eventual transformation of the pendant ester to the corresponding methyl group. With the key triene system in hand, metathesis-mediated bond reorganization could be investigated (Scheme 4).

Exposure of the ether bridged triene to the second-generation Grubbs catalyst led to a rapid reaction and the formation of the spiroannulated furan **11** in excellent yield. Overall, the reaction involves a ring-opening metathesis of the strained endocyclic double bond and two consecutive ring-closing metathesis reactions. Based on the direct and high-yielding conversion of **10**, a more difficult case was targeted that would deliver a seven-membered rather than six-membered D-ring surrogate as that found in IPI-926 (Scheme 5).

Scheme 5. Synthesis of a Cyclopamine Model with an Expanded D-Ring



Alkylation of 2-lithiofuran with 1-bromo-5-hexene gave the heterocycle **12**, which was taken on through the routes described above to the bicyclic ether **13**. Treatment of this triene with Grubbs' catalyst again led to a smooth reorganization to the highly substituted tetrahydrofuran **14**, albeit with a longer reaction time and slightly diminished yield as compared to the six-membered case. Overall, we have described an approach to the spirocyclic region of cyclopamine by pairing a furan Diels–Alder reaction with a domino metathesis process. Our current efforts are aimed at the synthesis of a fully functionalized DEF subunit of cyclopamine and the development of methods for the stereocontrolled annulation of an AB-ring system.

Acknowledgment. We are grateful to the National Science Foundation (CHE-0616760) for generous support of this work.

Supporting Information Available. Experimental procedures and full characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

(12) (a) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 636. (b) Novak, L.; Baan, G.; Marosfalvi, J.; Szantay, C. *Tetrahedron Lett.* **1978**, *19*, 487.