Synthesis of (-) - Indolactam V for the Total Synthesis of Cytoblastin

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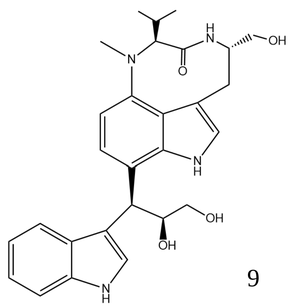
Objective

The objective of this research is to synthesize (-)-indolactam V for use in the total synthesis of cytoblastin.

Background

- Cytoblastin (9) is a low weight drug which can be used to treat diseases by modifying the body's immune response **[1]**.
- Currently, cytoblastin is increasingly being used as an effective treatment for Aids-HIV cancer, non-Hodgkins lymphoma, lung cancer, melanoma, testicular cancer, and vulva cancer **[1]** .
- Although cytoblastin is a useful drug, it is difficult and expensive to isolate from its natural source **[1]**.



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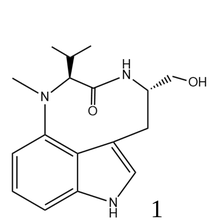
Cytoblastin

[1] KUMAGAI, HIROYUKI, et al. "Cytoblastin, a low molecular weight immunomodulator produced by Streptoverticillium eurocidicum." The Journal of antibiotics 44.9 (1991): 1029-1032.

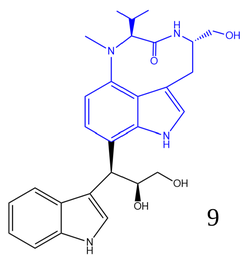
Motivation

- Current synthetic methods of producing cytoblastin have low yields and are not enantioselective, which makes cytoblastin difficult to manufacture or study.
- Developing a more reliable and enantioselective method of synthesizing cytoblastin would allow future researchers to easily study the medicinal properties of the molecule. This could potentially lead to the creation of new effective drugs for a variety of diseases.
- It has been proven that the stereochemistry in the upper half of cytoblastin is identical to (-)-indolactam V (1) **[2]**.



1

(-)-Indolactam V



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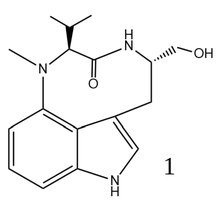
Cytoblastin

- Since (-)-indolactam V is a simpler molecule than cytoblastin, it is the goal of the May Group to first synthesize (-)-Indolactam V (1) from 4-bromoindole (2) and then use modern reactions to synthesize Cytoblastin (9) .



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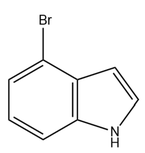
(-)-indolactam V

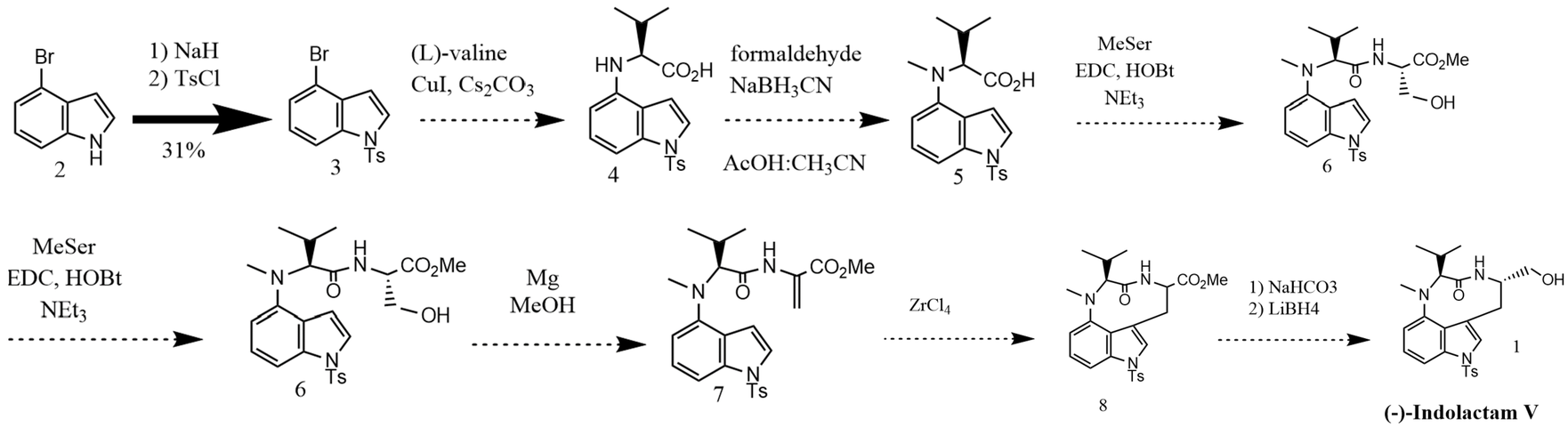


2

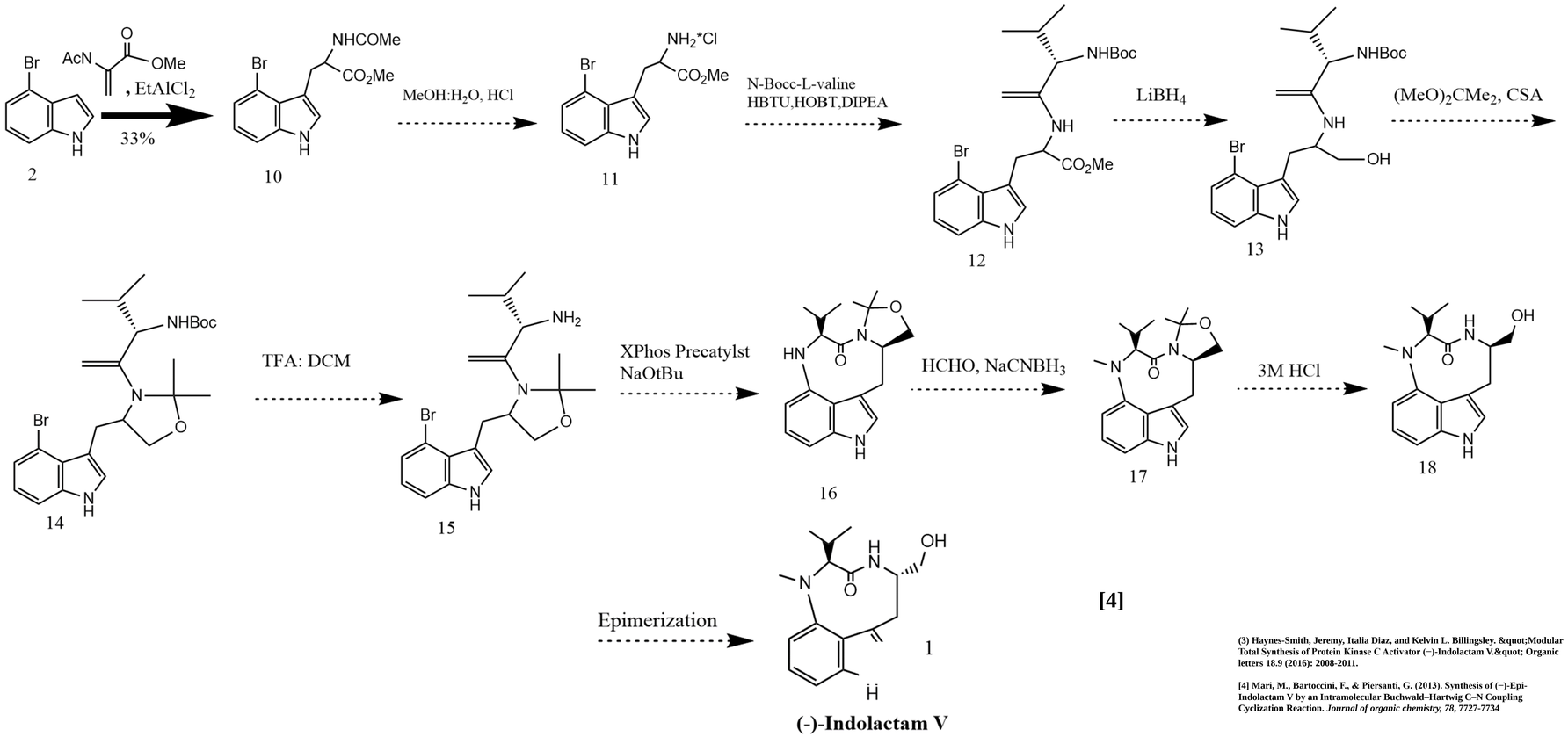
4-bromoindole

[2] Moreno, Ofir A., and Yoshito Kishi. "Total synthesis and stereochemistry of cytoblastin." Journal of the American Chemical Society 118.34 (1996): 8180-8181.

Synthesis Route 1



Synthetic Route 2



[4]

(3) Haynes-Smith, Jeremy, Italia Diaz, and Kelvin L. Billingsley. "Modular Total Synthesis of Protein Kinase C Activator (−)-Indolactam V." Organic letters 18.9 (2016): 2008-2011.

[4] Mari, M., Bartoccini, F., & Piersanti, G. (2013). Synthesis of (−)-Epi-Indolactam V by an Intramolecular Buchwald–Hartwig C–N Coupling Cyclization Reaction. *Journal of organic chemistry*, *78*, 7727-7734

Results and Discussion

- Synthetic Route 1 was first attempted due to the low amount of steps and high reported overall yield. However, the Cu mediated N-arylation coupling between molecules 2 and 3 failed.
- Synthetic Route 2 was chosen as an alternative since it used more robust reactions.
- Currently work is being done to synthesize bromoindole11.

Conclusion and Future Work

- In conclusion, the route in Scheme 1 was abandoned due to a failure in the N-arylation coupling reaction between molecule 2 and 3.
- Current work is focused on synthesizing molecules 9 and 10 in higher yields, while successfully synthesizing molecule 11.
- In the future, more molecules in the route are hoped to be synthesized successfully . Once the route reaches molecule 15, work will begin on the Xphos precatylst.

Acknowledgments

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