A New Approach to the Core of Flinderole C

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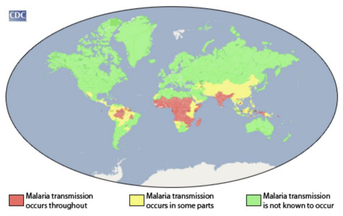
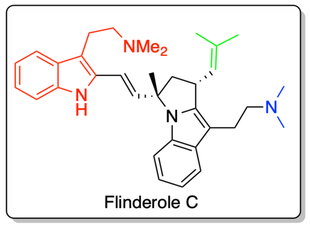
Introduction

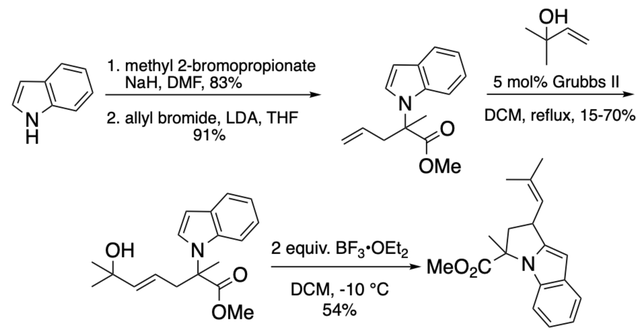
The flinderoles A-C are a class of anti-malaria bisindole alkaloids from plants of the *Flindersia* genus. Flinderole C was specifically from the Papua New Guinean plant called *F. amboinensis* and is the most potent antimalarial of the group. Malaria is a parasitic infectious disease usually found in hot tropical regions of the world, such as parts of Africa. It is estimated that nearly half the world's population lives in an area where it is endemic. Most people affected by malaria are young children, pregnant women and travelers/immigrants. Furthermore, malaria was estimated to have caused over 600,000 deaths in 2020. The parasite *P. falciparum* causes most infections, and its vector is the female *Anopheles* mosquito.



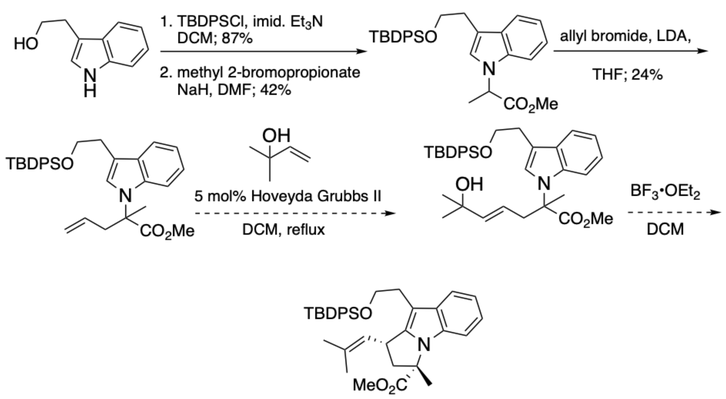


While measures to limit the spread of the disease lessen its impact, there is still a need for new treatments. There are numerous drugs and naturally occurring compounds employed to treat malaria, but many have lost their effectiveness due to drug resistance. The flinderoles could be a platform to develop new drugs as they possess a unique mode of action. In particular, flinderole C has been shown to treat the Dd2 strain of the parasite that is resistant to chloroquine, a frontline treatment of malaria. Going forward, the need for more treatments for malaria will only increase as the parasite continues to evolve. To meet this need, flinderoles C and related compounds must be synthesized and tested to identify more potent drugs.

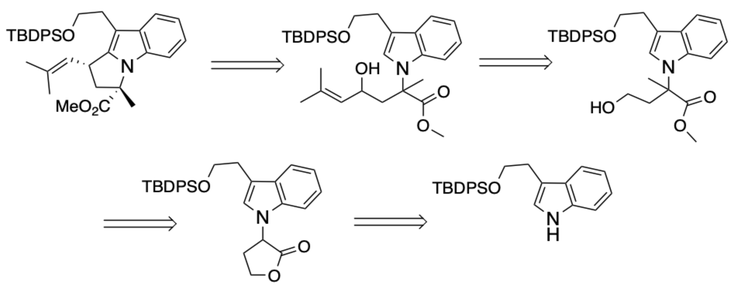
Synthesis of a Simplified Flinderole C Core



Failed Approach to the Flinderole C Core



Retrosynthetic Plan for Flinderole C Core



Acknowledgements

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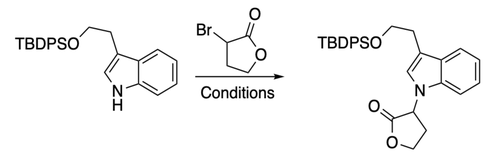
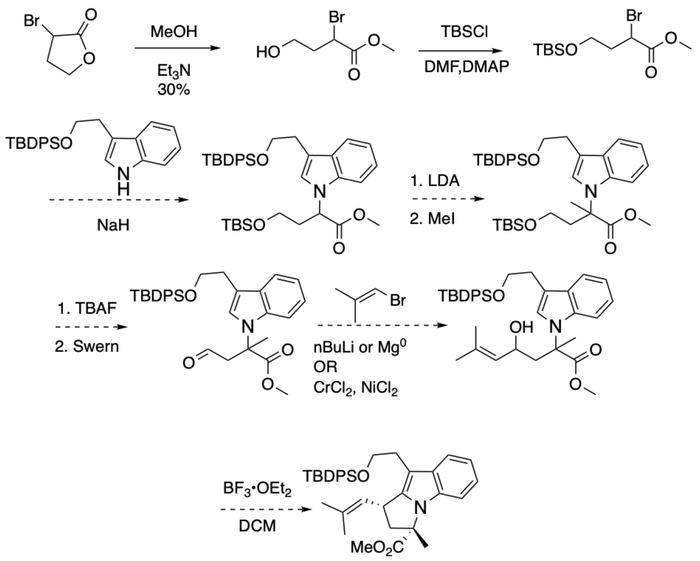
Addition to the Lactone



Entry	Conditions	Temp. (°C)	Result
1	NaH, DMF	0°	No Product
2	NaH, DMF	85°	No Product
3	K_2CO_3, KI, DMF	85°	No Product
4	K_2CO_3, KI, MeCN	85°	No Product
5	Cs_2CO_3, DMF	85°	No Product

Proposed Completion of Flinderole C Analogues



Conclusion

- Indole addition to the bromo lactone was attempted under varying conditions but was not successful.
- The approach has been modified to open the lactone first followed by indole addition. This will provide access to the required alcohol.
- Studies are underway to determine the best condition for the lactone opening and subsequent indole addition.