Enantioselective Synthesis of Cyclic Ethers by Use of Asymmetric Carbenoid and Tsuji-Trost Allylation Reactions: Towards the Total Synthesis of Zoapatanol

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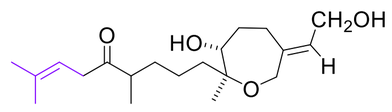
1. Introduction

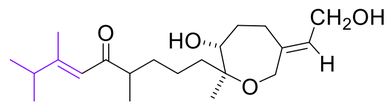
- In 1979, Levine and coworkers identified **bioactive diterpenoids zoapatanol** (**1**) and **montanol** (**2**) from the zoapatle plant, ***Montanoa Tomentosa***[1]
- Traditionally used in tea form for antifertility, labor and menstruation inducing abilities
- They also produce an anxiolytic-like effect[2]
- Despite these biological activities the mechanisms of action remain elusive - interesting target for synthesis

Montanoa Tomentosa

- Both feature a core **oxepane** moiety but have **different side chians**[2]
- Zoapatanol (**1**) has most **promising bioactivity**
- Seven total synthesis of **1** have been reported, only two have shown enantioselectivity[2,3]
- The efficient synthesis of enantiopure **1** is necessary to further study its biological effects



Zoapatanol (**1**)



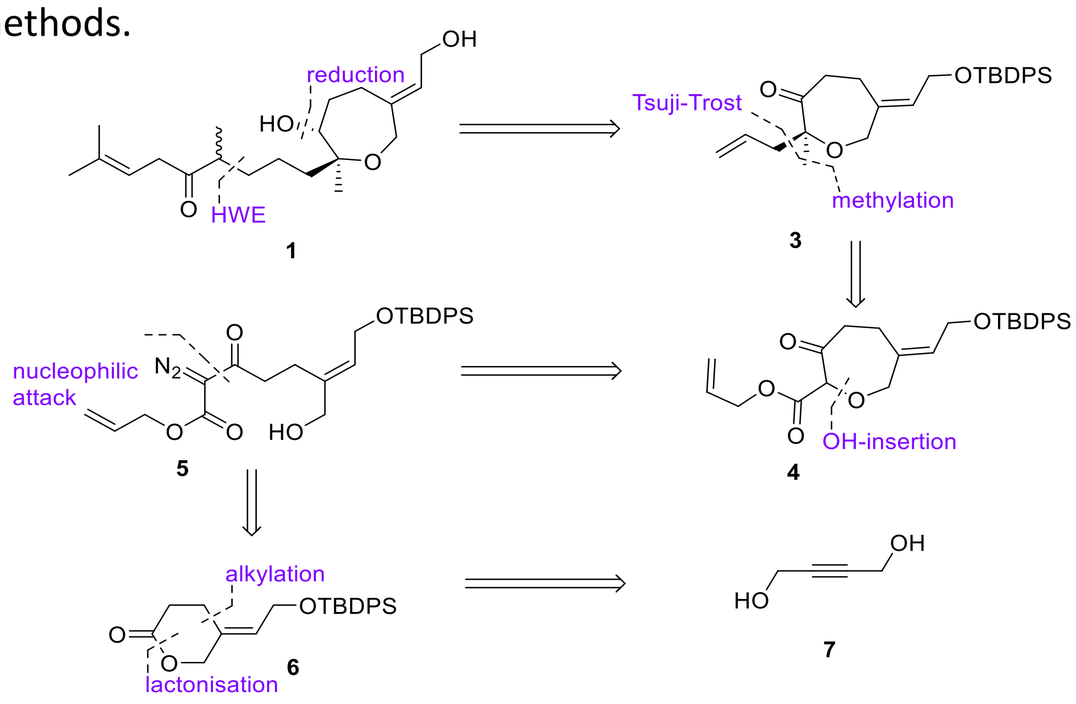
Montanol (**2**)

2. Aim

- Previous work in the Clark group identified a viable route the **oxepane** core, but with low yields and difficulties elaborating the side chain
- This work will build on previously attempts to develop an efficient and stereoselective route to **1**, enabling further biological testing

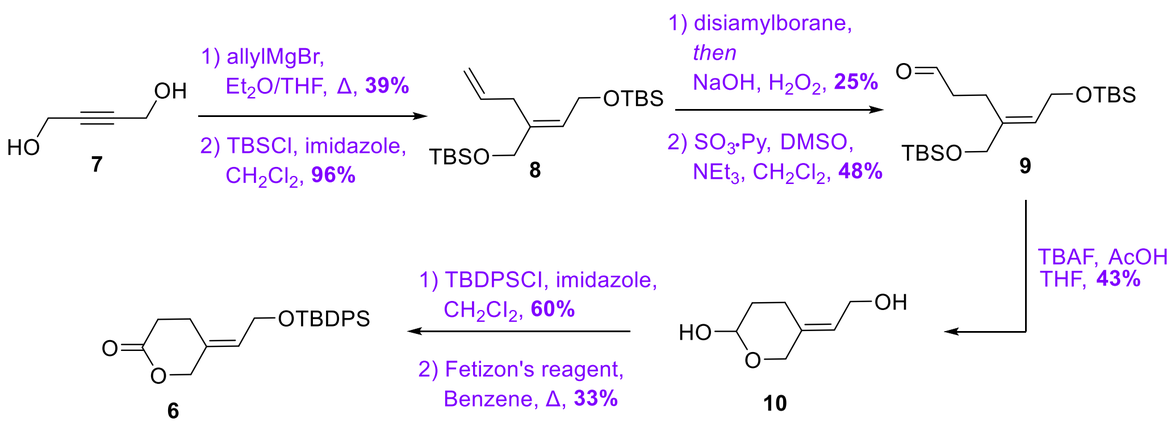
3. Retrosynthetic Analysis of 1

1 could be synthesized by elaborating **3** and a ketone reduction. Intermediate **3** is accessed by Tsuji-Trost allylation from allyl ester **4**, which made by OH-insertion to a carbene derived from **5**. A ring opening of lactone **6** with lithiated allyl diazoacetate gives **5**.[4] Lactone **6** can be generated from 1,4-butynediol **7** using established methods.



4. Result

- The allyl group in **8** was installed by Grignard reaction with **7** followed by TBS protection of the diol in good yield
- Hydroboration/oxidation of **8** gave a terminal alcohol which was oxidised by a Parikh-Doering reaction to give aldehyde **9**
- TBAF-mediated desilylation of **9** gave a diol which spontaneously ring-closed to lactol **10**
- The primary alcohol in **10** is selectively protected using TBDPSCl
- Finally, lactol **10** was converted to lactone **6** using Fetizon's reagent (Ag_2O on Celite) without the need for purification
- Compounds were confirmed by spectroscopic techniques **NMR**, **HRMS** and **IR**



5. Conclusion

- The aim is to synthesise enantiopure **1** to generate material for biological testing
- Thus far, small scale reactions have been successful to form lactone **6** using methods previously established in the Clark group
- With the conditions now developed, these steps will be scaled up to provide adequate material for further synthetic efforts

6. Future Work

Going forward, the synthetic effort will focus on generating precursor **3** using the route shown below.

This strategy follows an OH-insertion precursor from **6** to form the oxepane ring fragment **12**. This is essential for the installation of the side chain which will be achieved in the near future.

7. Reference

1) S. D. Levine et al, *J. Am. Chem. Soc.*, **1979**, 101, 3404-3405
2) D. W. Hahn et al, *Contraception.*, **1984**, 30, 39-53
3) J. Cossy et al, *Org. Lett.*, **2004**, 6, 13, 2149–2151
4) J. Skardon-Duncan, **2019**

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