

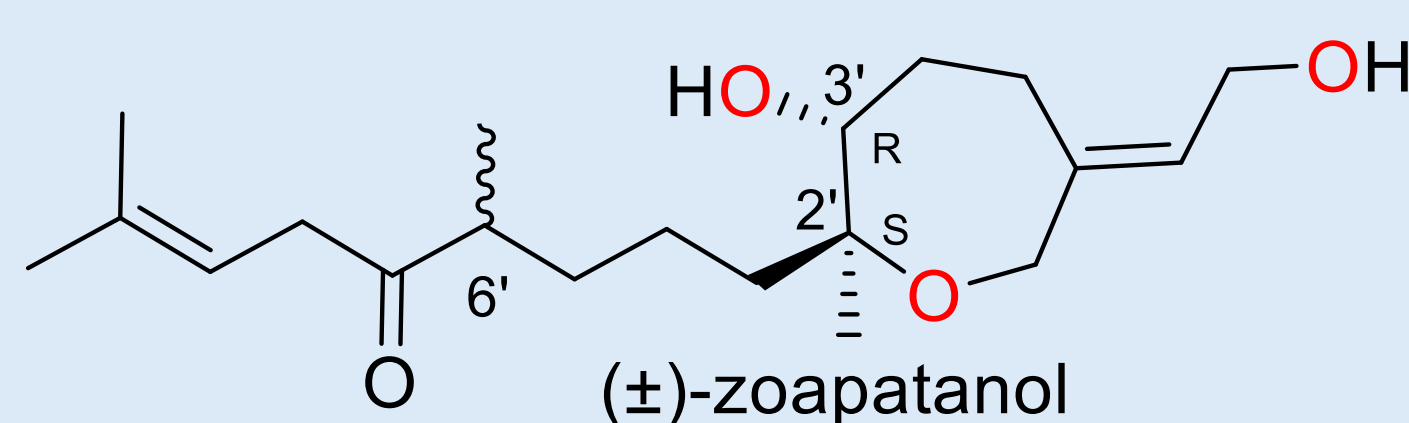
INTRODUCTION

- Class of diterpenoid oxepane natural product
- Isolated in 1979 from the Mexican native plant *Montanoa tomentosa*¹
- Biological applications- gynecology and obstetrics
- Zoapatanol** metabolites were found to be responsible for bioactivity
- There have been seven total synthesis in racemic form with only two showcasing an asymmetric approach

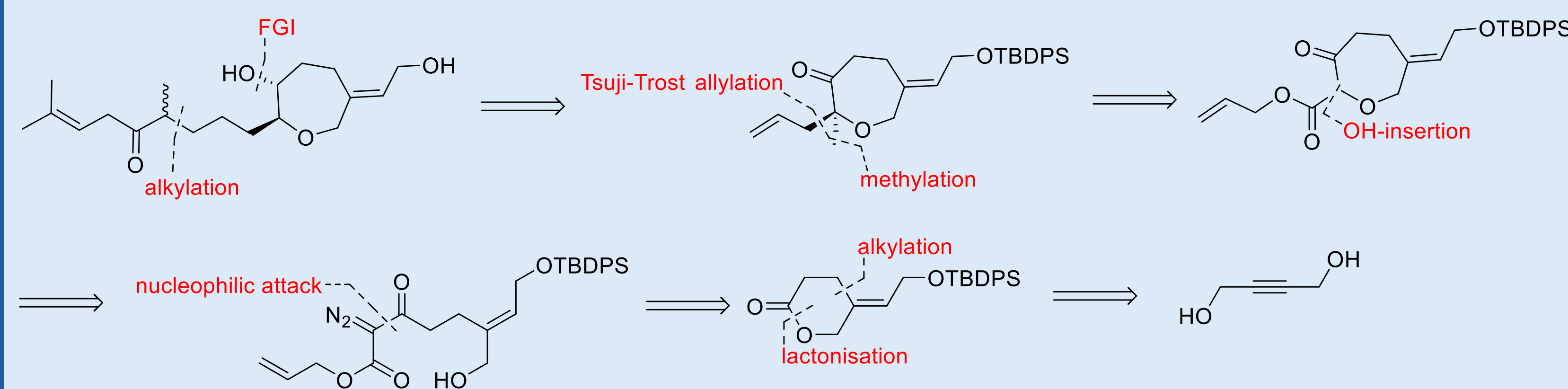


Key Structural features:

- Quaternary center at C2'
- Adjacent stereocenter at C3'
- 1:1 mixture of epimers at C6' – diastereomeric mixture
- Exocyclic *E*-olefin and the oxepane

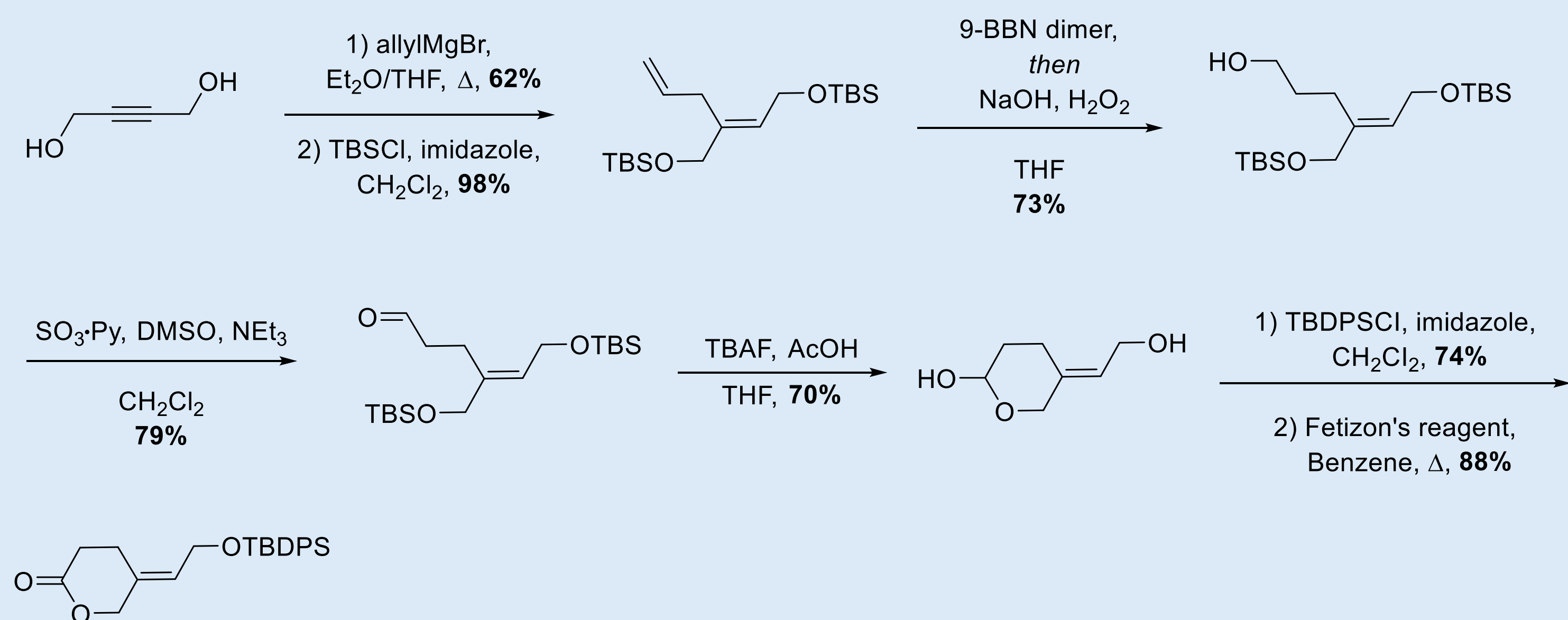


RETROSYNTHETIC APPROACH



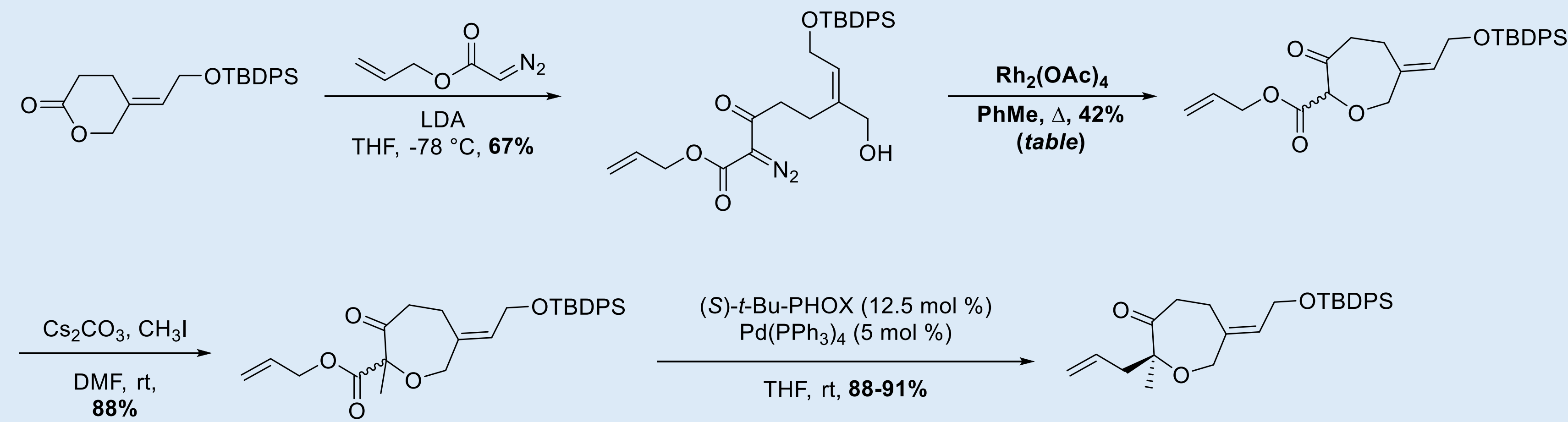
RESULTS AND DISCUSSION

1. ROUTE TOWARDS LACTONE FORMATION



- Grignard reaction produces the diol with the required *E*-olefin configuration
- TBDPSCl protection installed to prevent by-product formation in following steps

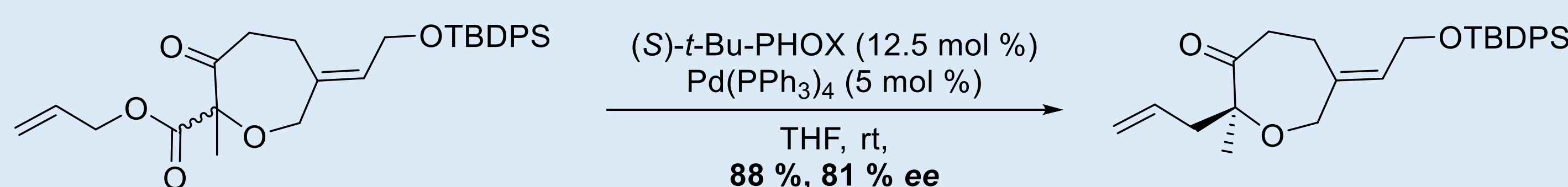
2. ROUTE TOWARDS ALLYLATED OXEPANE



Entry	Catalyst	Solvent	Yield (%)
1	Rh ₂ (oct) ₄ , 2.5 mol%	PhMe	42
2	Rh ₂ (oct) ₄ , 10 mol%	CH ₂ Cl ₂	19
3	Rh ₂ (oct) ₄ , 10 mol%	PhMe	26
4	Rh ₂ (tfacam) ₄ , 10 mol%	CH ₂ Cl ₂	22
5	Rh ₂ (tfacam) ₄ , 5 mol%	PhMe	29
6	Rh ₂ (TPA) ₄ , 10 mol%	CH ₂ Cl ₂	21
7	Rh ₂ (TPA) ₄ , 5 mol%	PhMe	32
8	Ni(acac) ₂ , 10 mol%	CH ₂ Cl ₂	¹ H NMR: SM
9	Ni(acac) ₂ , 10 mol%	PhMe	23
*10	BF ₃ .OEt ₂ , 1.21 equiv	CH ₂ Cl ₂	¹ H NMR: SM

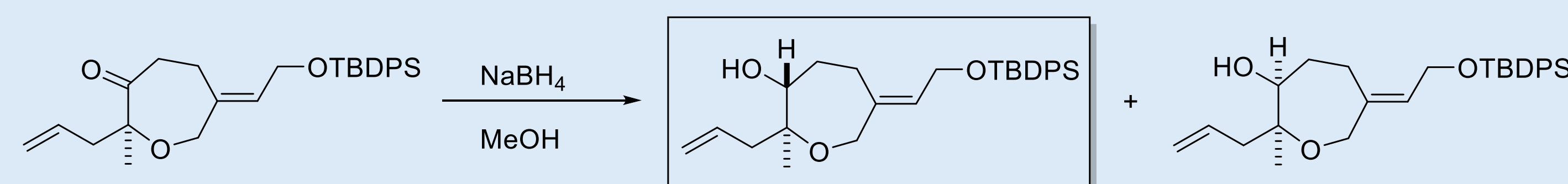
*Reaction performed at 0 °C – rt

3. TSUJI TROST ALLYLATION REACTION



- Adapted from literature by Stoltz and colleagues.²
- Facilitated by using a chiral ligand and palladium catalyst to set the desired α-quaternary stereocentre.
- Key feature of Clark synthesis- widely employed by past and present researchers within the group.³
- Research performed by Clark and coworkers demonstrate the functionalization of medium-sized (seven and eight-membered) cyclic ethers with excellent yields and enantioselectivity.⁴

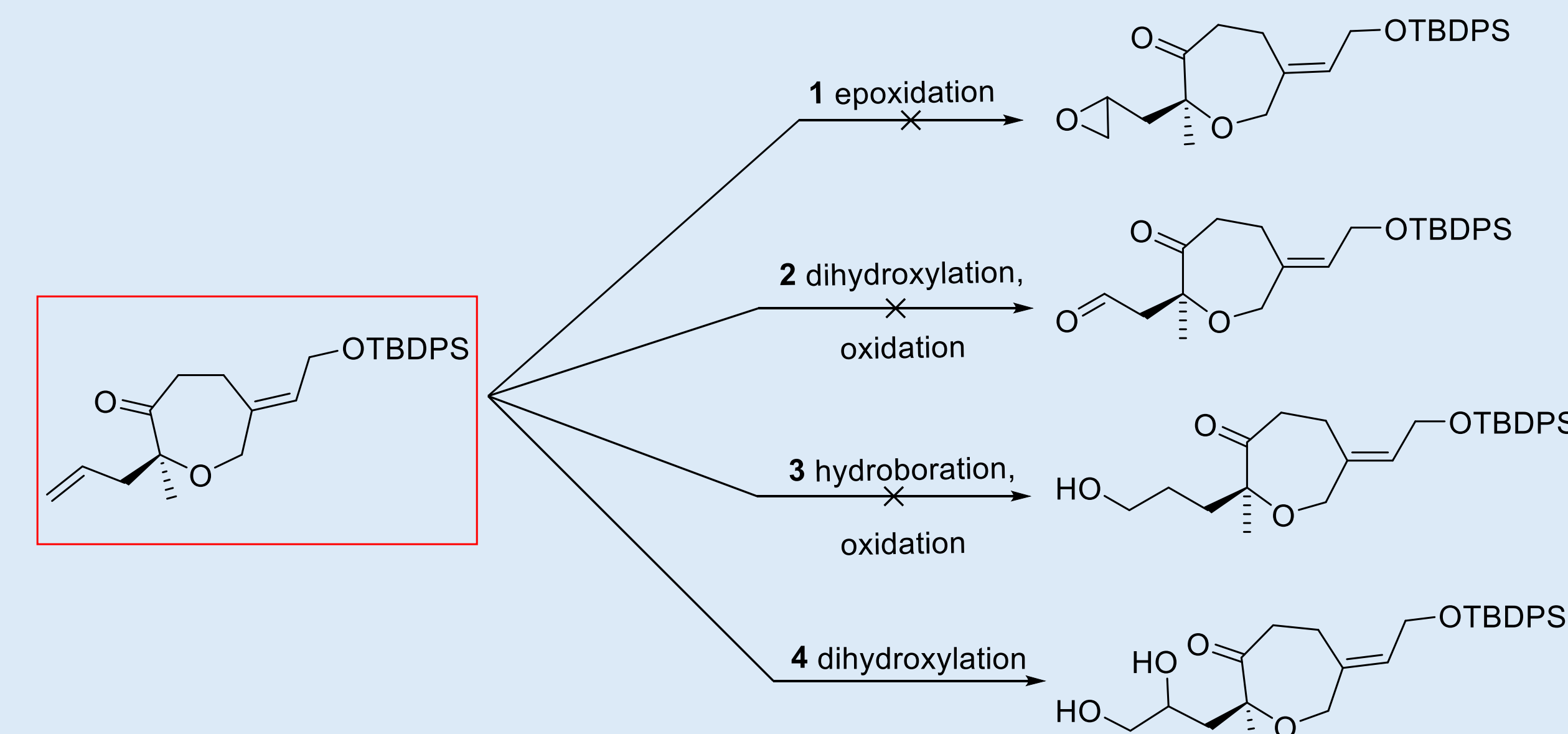
STEREOSELECTIVE REDUCTION



- 65 % yied
- Diastereoisomers are separable by HPLC

4. SIDE CHAIN ELABORATION

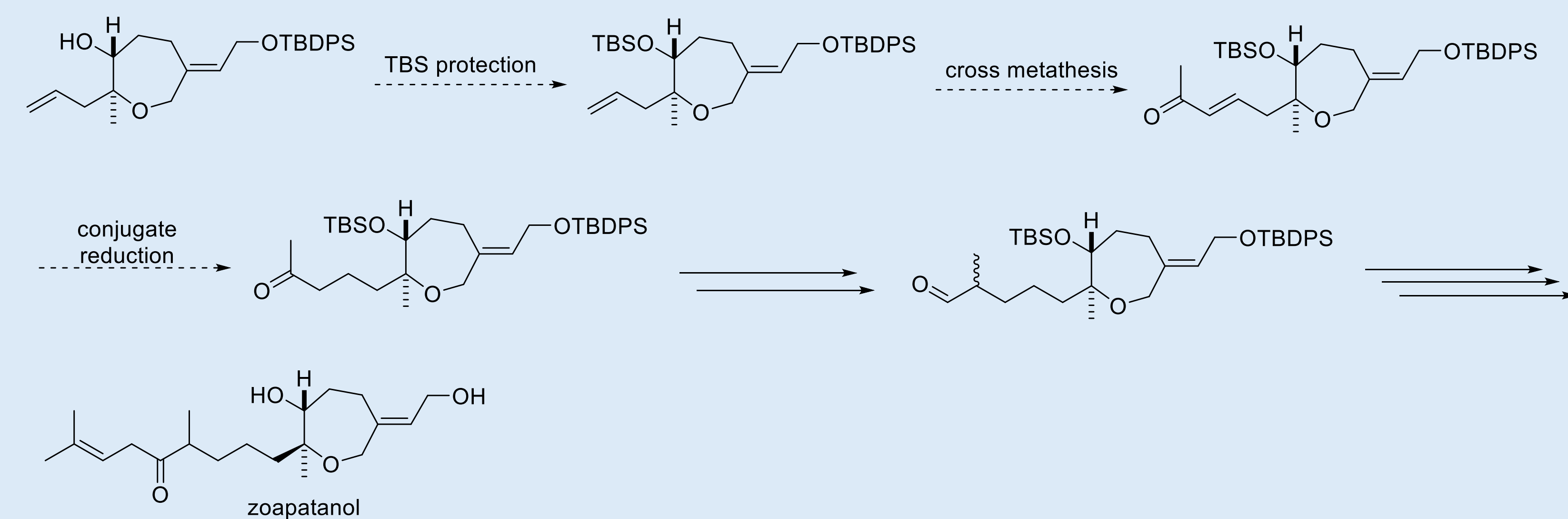
Alkene Cleavage Approach



Entry	Conditions	Outcome
1	1.3 equiv. mCPBA, CH ₂ Cl ₂	SM recovery
2	5 mol % OsO ₄ , 1.1 equiv. NMO, NaIO ₄ , IPA:H ₂ O	Overreaction by ¹ H NMR
3	disiamylborane 7 equiv., NaOH, H ₂ O ₂ , THF	SM recovery
4	5 mol % OsO ₄ , 1.1 equiv. NMO, THF:H ₂ O	15 % + SM

- Replicating Upjohn dihydroxylation reaction **4** generated a complex mixture of products

FUTURE WORK



REFERENCES AND ACKNOWLEDGEMENTS

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- Behenna, D. C.; Stoltz, B. M, *J. Am. Chem. Soc.*, **2004**, 126 (46), 15044-15045.
- J. Skardon-Duncan, PhD Thesis, University of Glasgow **2019**.
- J. Skardon-Duncan, M. Sparenberg, A. Bayle, S. Alexander, J. S. Clark, *Org. Lett.* **2018**, 20, 2782-2786.

- **Abbreviation:** ee- enantioselectivity

Clark group
Henderson lab

GSK

