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SYNTHESIS OF CRYPTOCARYOL VIA AN ITERATIVE EPOXIDE-OPENING BASED STRATEGY

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INTRODUCTION

- Natural polyacetate compound
- 5,6-dihydro- α -pyrones with repeating 1,3-polyol moieties
- Isolated from the bark of the South African plant, *Cryptocarya latifolia*

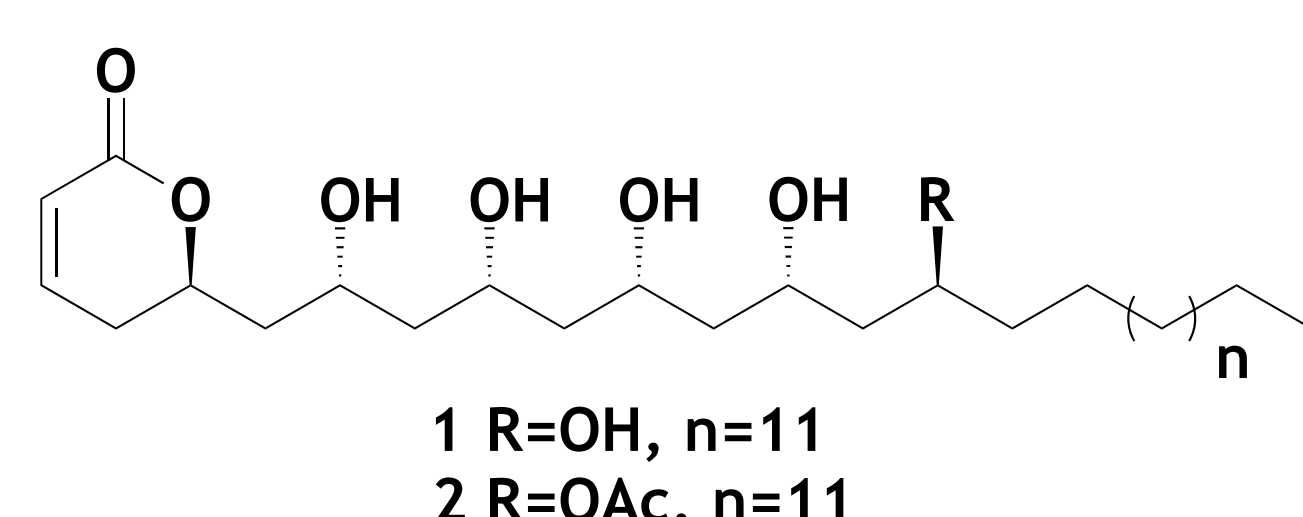


Fig. 1: Elucidated structure of cryptocaryol A (1) and B (2)
Grkovic *et al.* 2011, Wang *et al.* 2013

TUMOUR SUPPRESSOR PROTEIN STABILIZER

Grkovic *et al.* 2011

- Cryptocaryols shown to be a stabilizer of programmed cell death 4 (Pdc4) protein
- Pdc4 is a novel tumour suppressor protein
- Down regulation of Pdc4 expression linked to onset of human tumours
- Stabilization of Pdc4 levels represent an attractive potential anticancer therapy

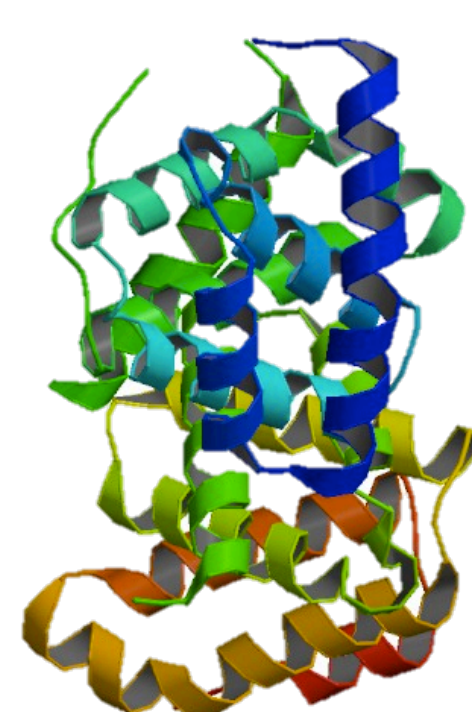


Fig. 2: 2.8 Å crystal structure of Pdc4
Loh *et al.* 2009

α -TUBULIN INHIBITOR

Carda *et al.* 2013

- Pirotenin, a 5,6-dihydro- α -pyrone, found to be a potent inhibitor of α -tubulin
- Conjugated C2-C3 π -bond and hydroxy group at C9 are essential for biological activity
- Cryptocaryols represent a potential pirotenin analogue for anticancer therapy

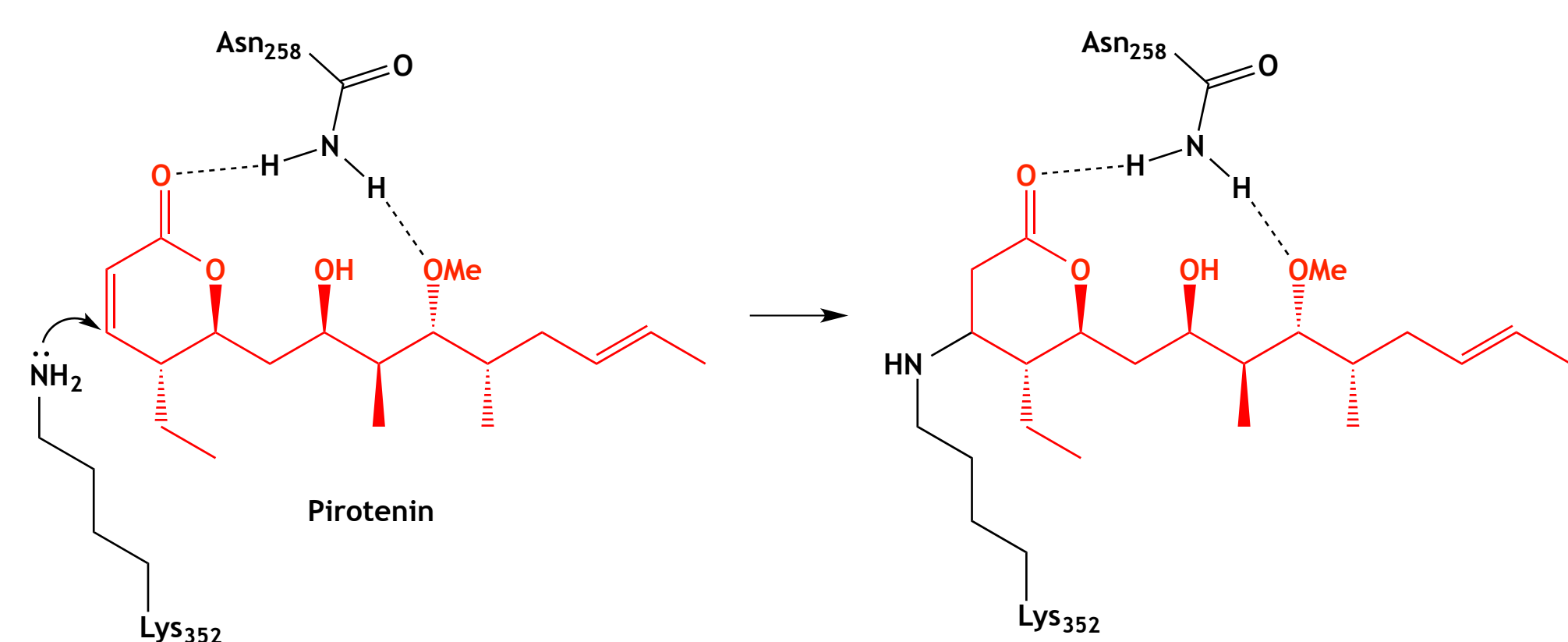


Fig. 3: Proposed Michael-type addition of α -tubulin Lys352 to Pirotenin
Carda *et al.* 2013

TOTAL SYNTHESIS

Wang *et al.* 2013

- 23-step total synthesis of cryptocaryol A from commercially available 5-hexyn-1-ol
- Achieved synthesis of only *syn* stereoconfigured polyacetates

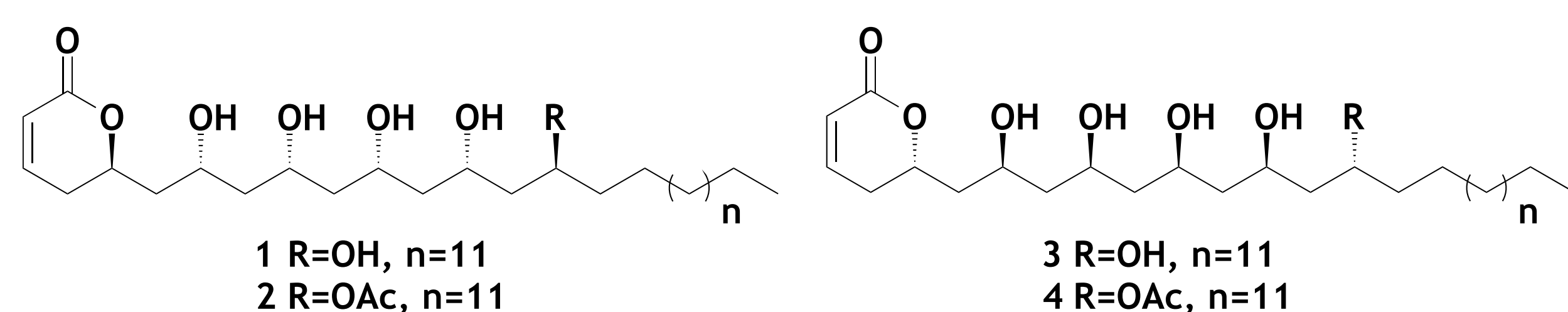


Fig. 4: Synthesized cryptocaryol analogues with all *syn* stereoconfigured polyacetates
Wang *et al.* 2013

OBJECTIVE

- Synthesize cryptocaryol analogues from 1,4-butanediol
- Use an iterative epoxide-opening based strategy to access both *syn* and *anti* stereoconfigured polyacetates
- Characterize new compounds by high resolution mass spectrometry and ^1H and ^{13}C Nuclear Magnetic Resonance spectroscopy.

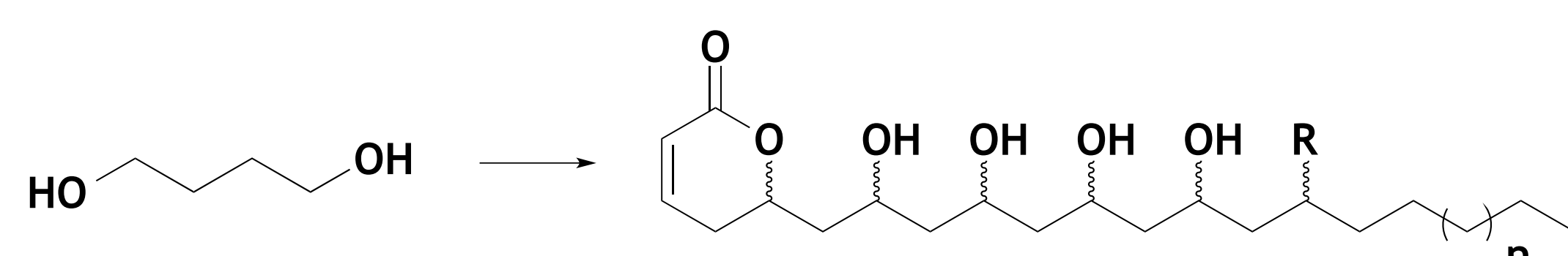


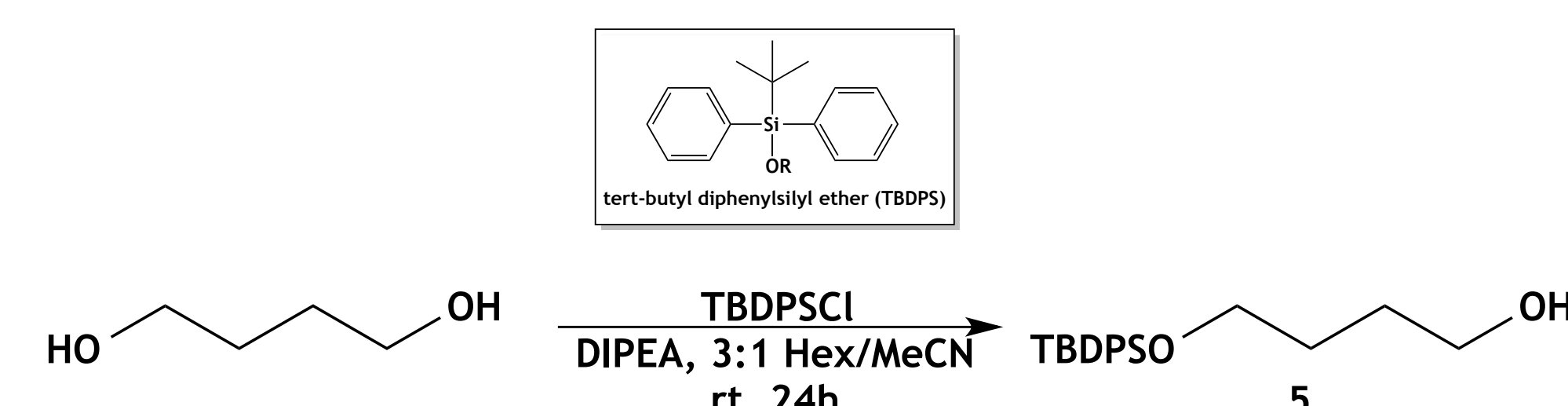
Fig. 5: Synthesis of cryptocaryol analogues from 1,4-butanediol

RESULTS

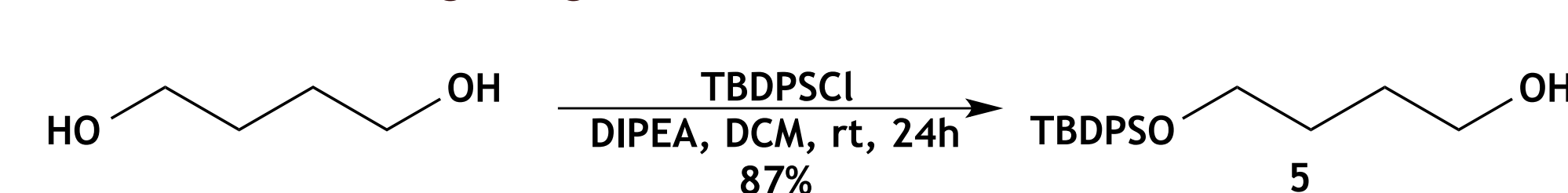
MONOSYLATION OF 1,4-BUTANEDIOL

Two strategies were employed for monosilylation:

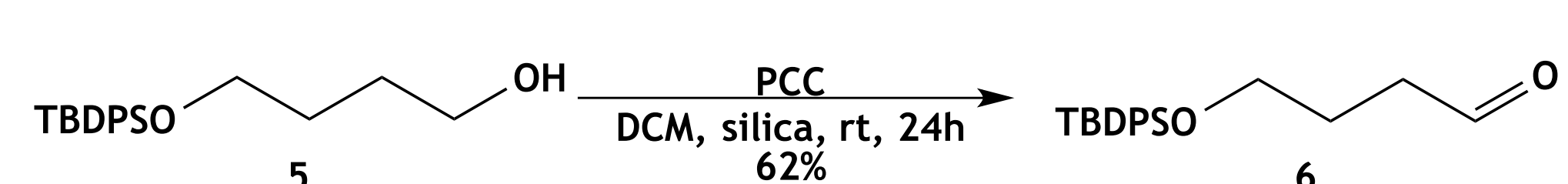
- Use of binary solvent system as described by Wilke *et al.* 2014



- Use of TBDS as limiting reagent with vast excess of 1,4-butanediol



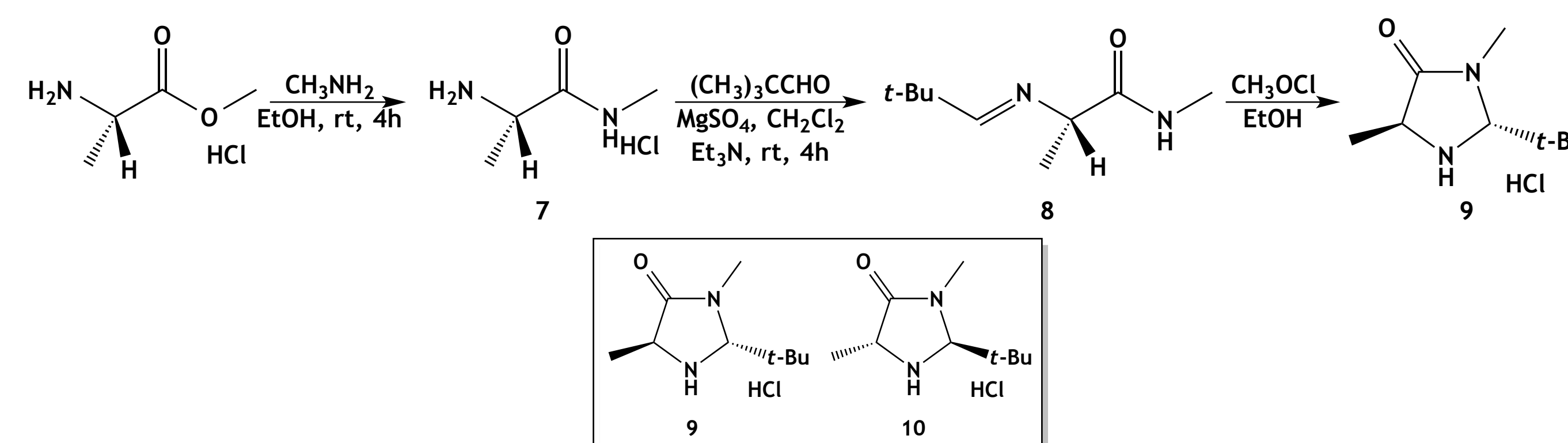
ALCOHOL OXIDATION



PREPARATION OF MACMILLAN'S CATALYST

Graham *et al.* 2011

- Successfully synthesized both enantiomers for use in enantioselective α -chlorination



Synthesized MacMillan's enantioselective α -chlorination catalyst

ENANTIOSELECTIVE EPOXIDE FORMATION

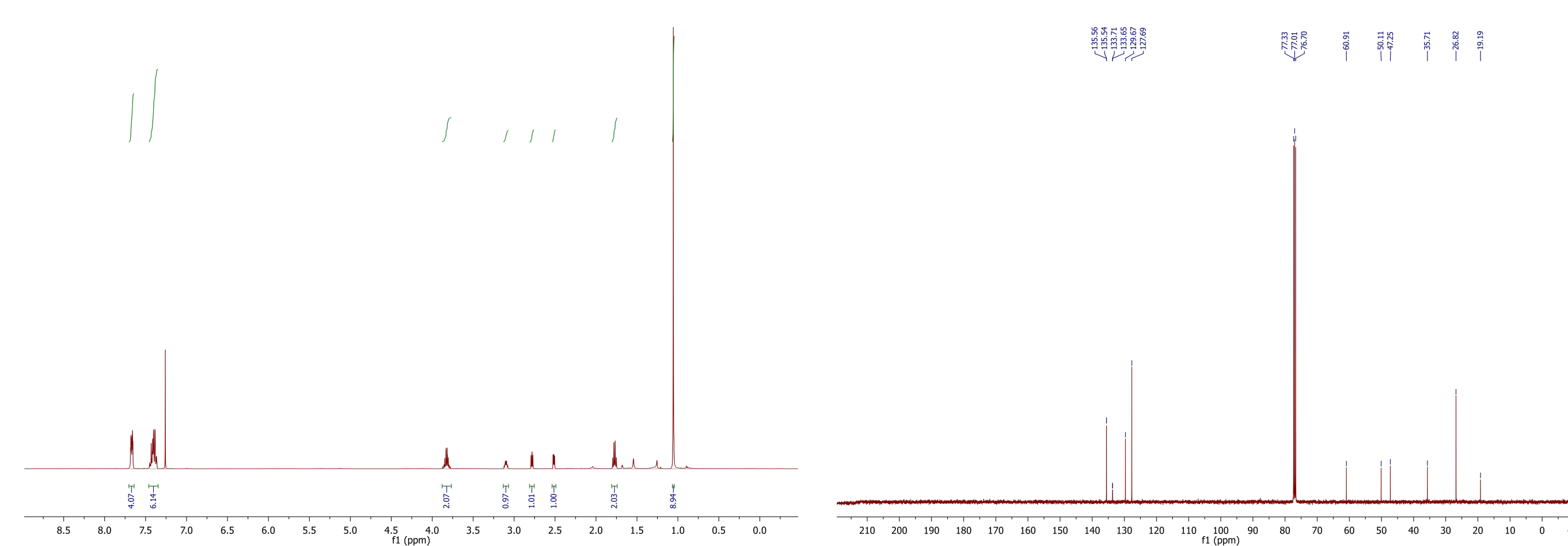
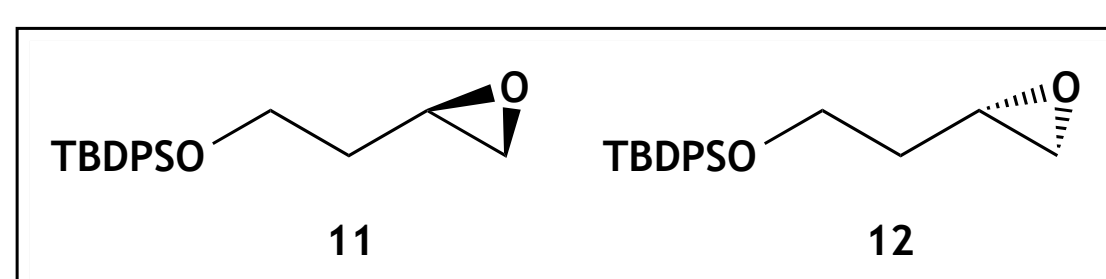
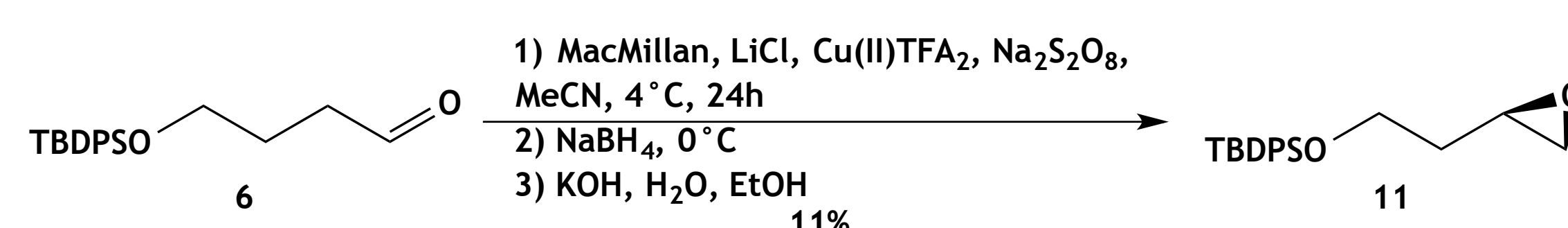


Fig. 8: ^1H , ^{13}C & HSQC NMR spectra of epoxide 11

SYNTHETIC SCHEME

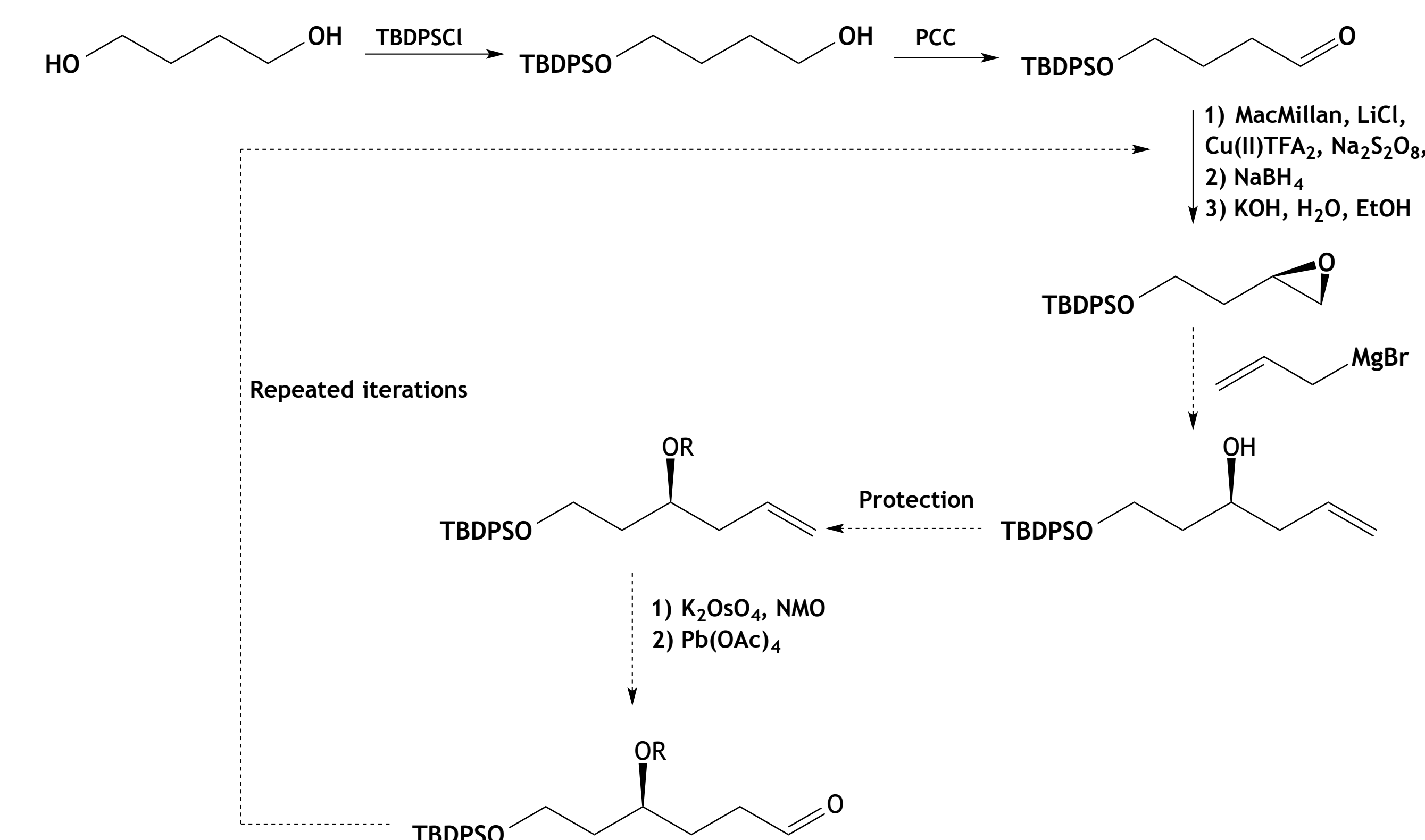


Fig. 6: Stereoselective synthesis of 1,3-polyol moieties

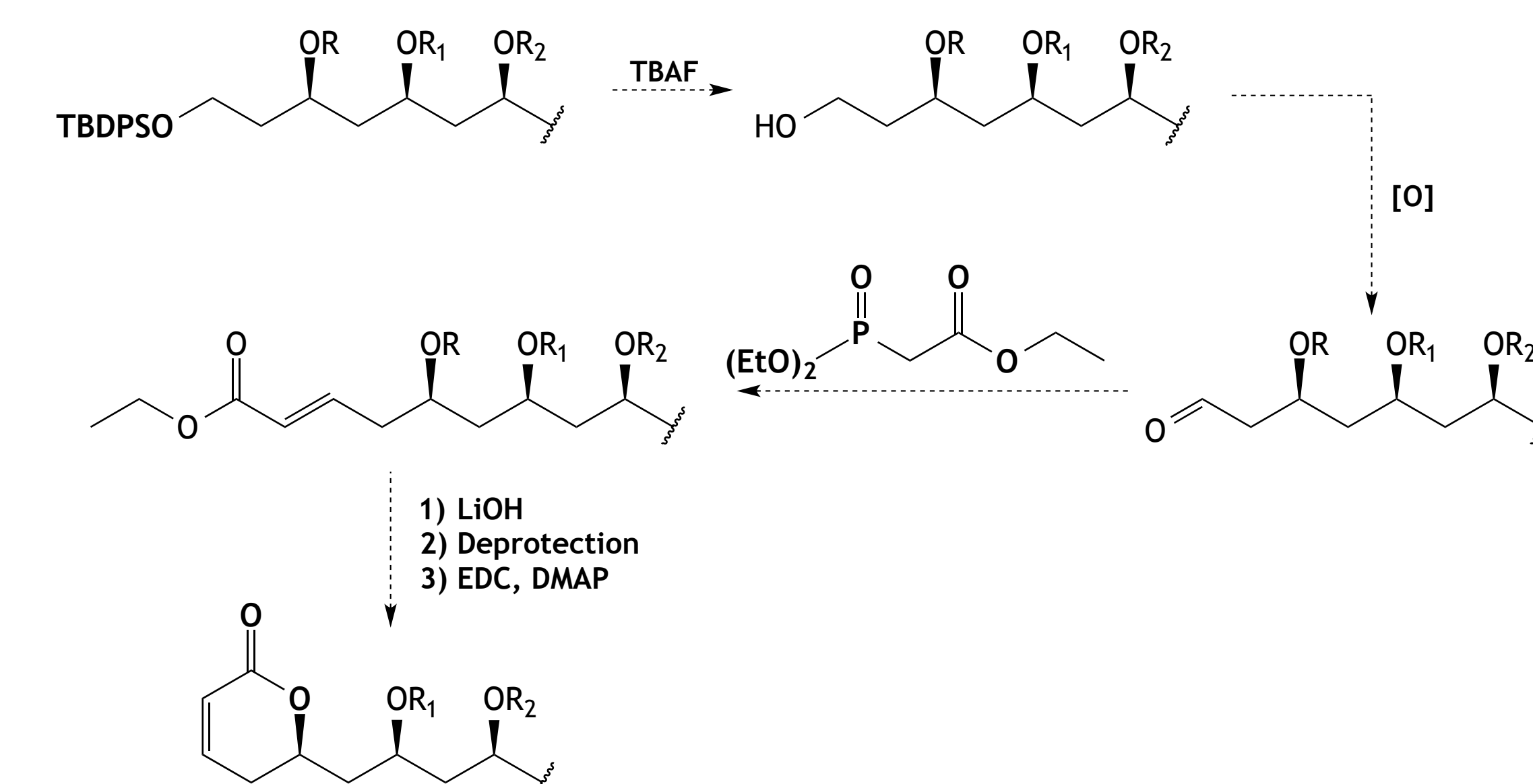


Fig. 7: Installation of dihydropyrone ring

CONCLUSION AND FUTURE DIRECTION

- Achieved successful stereoselective synthesis of epoxide 11 and 12
- Achieved successful characterization of epoxide 11 and 12 via:
 - ^1H nuclear magnetic resonance
 - ^{13}C nuclear magnetic resonance
 - High resolution electron impact mass spectroscopy
- Perform more iterations of epoxide-opening based total synthesis
- Install dihydropyrone ring to complete synthesis of cryptocaryol analogues
- Perform structure-activity relationship (SAR) studies
 - Evaluate Pdc4 stabilizing ability
 - Evaluate α -tubulin inhibition ability

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