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А-31

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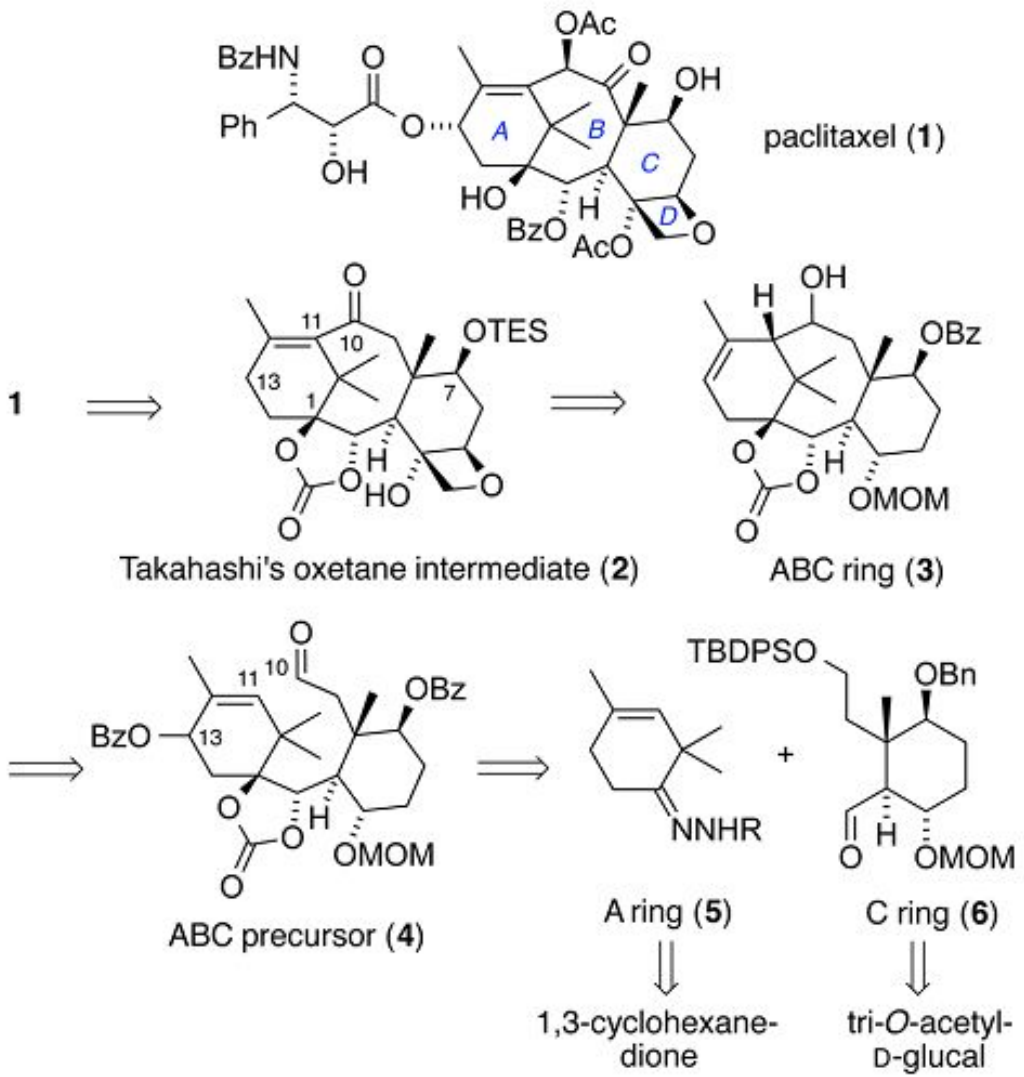
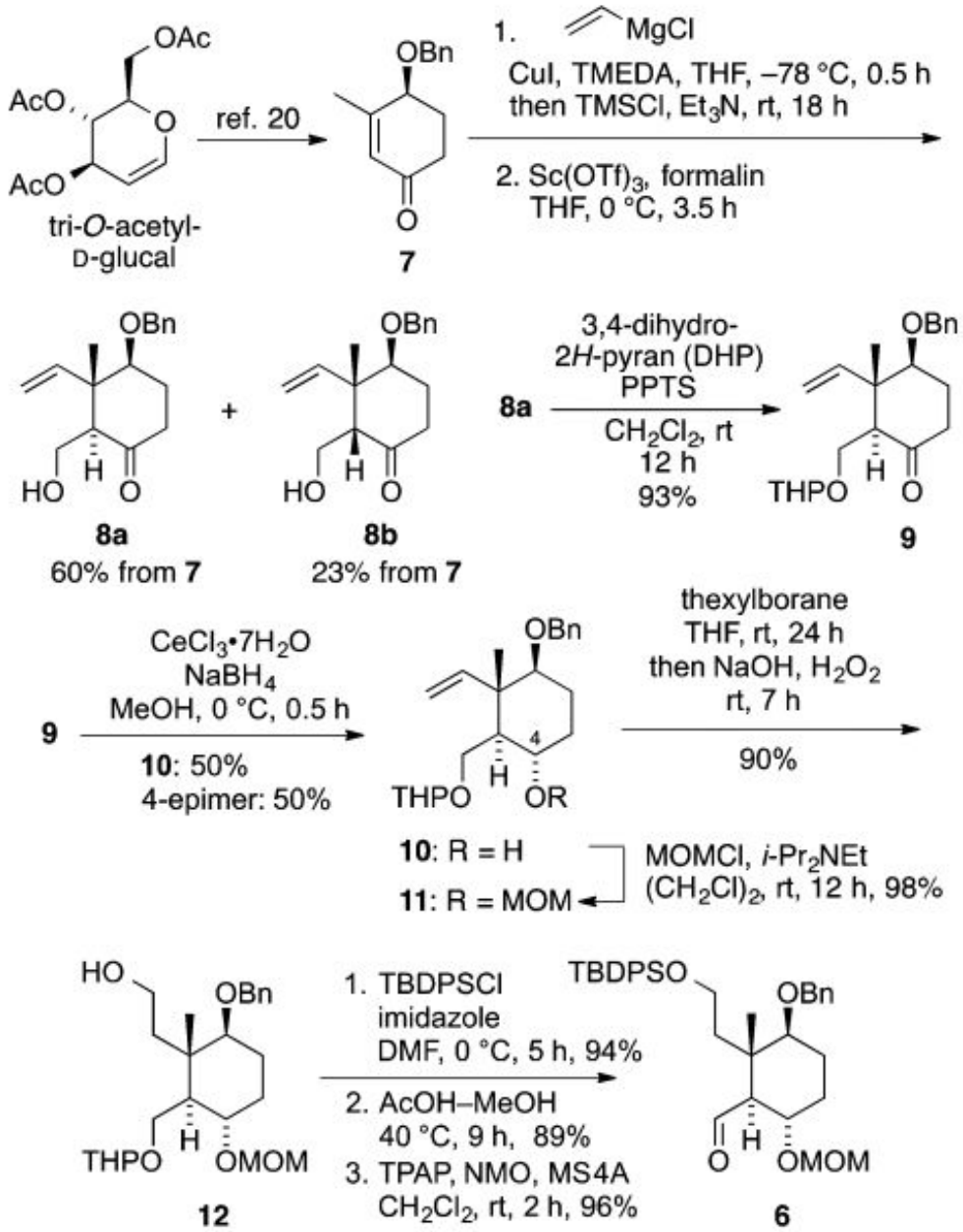
Synthesis of Paclitaxel.
1. Synthesis of the ABC Ring of Paclitaxel by SmI_2-Mediated Cyclization
2. Construction of the ABCD Ring and Formal Synthesis

08.12.2015

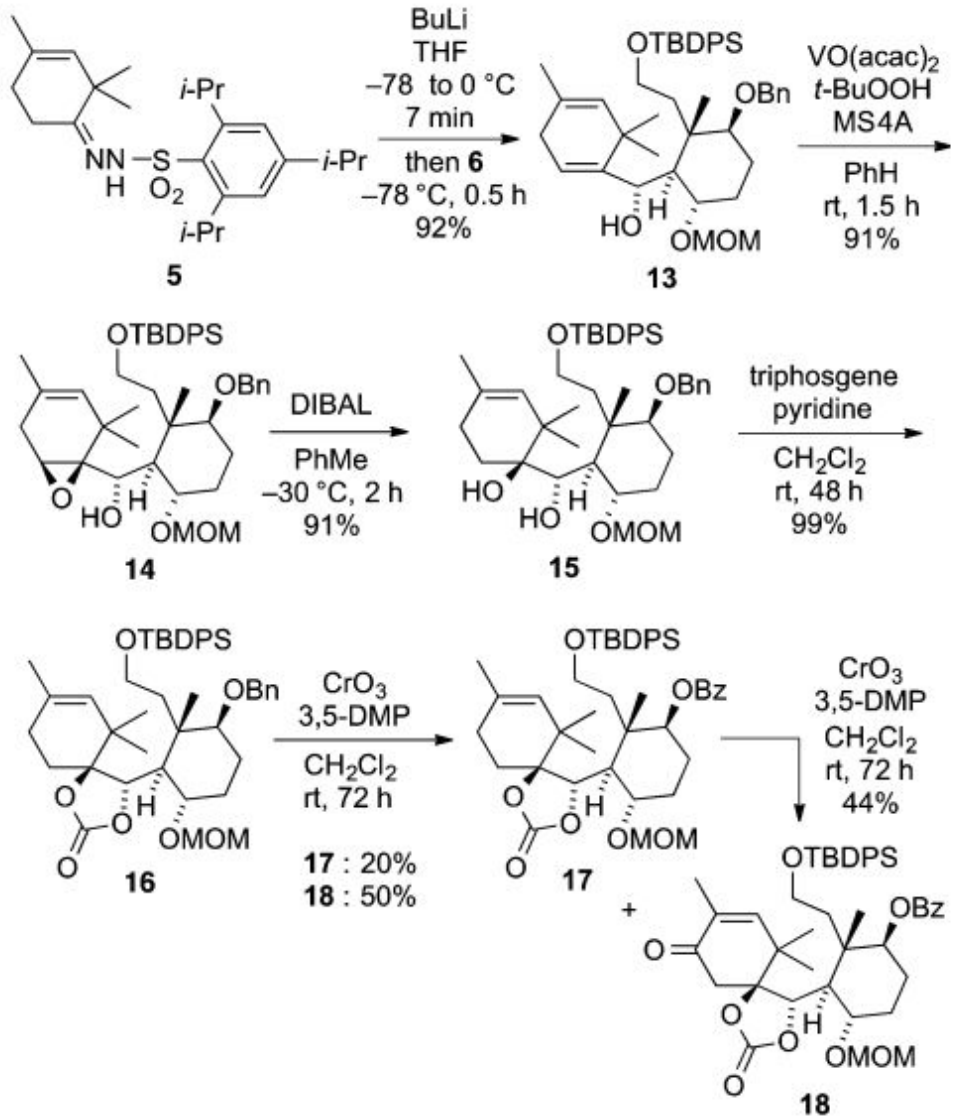
Retrosynthetic analysis of paclitaxel (1)



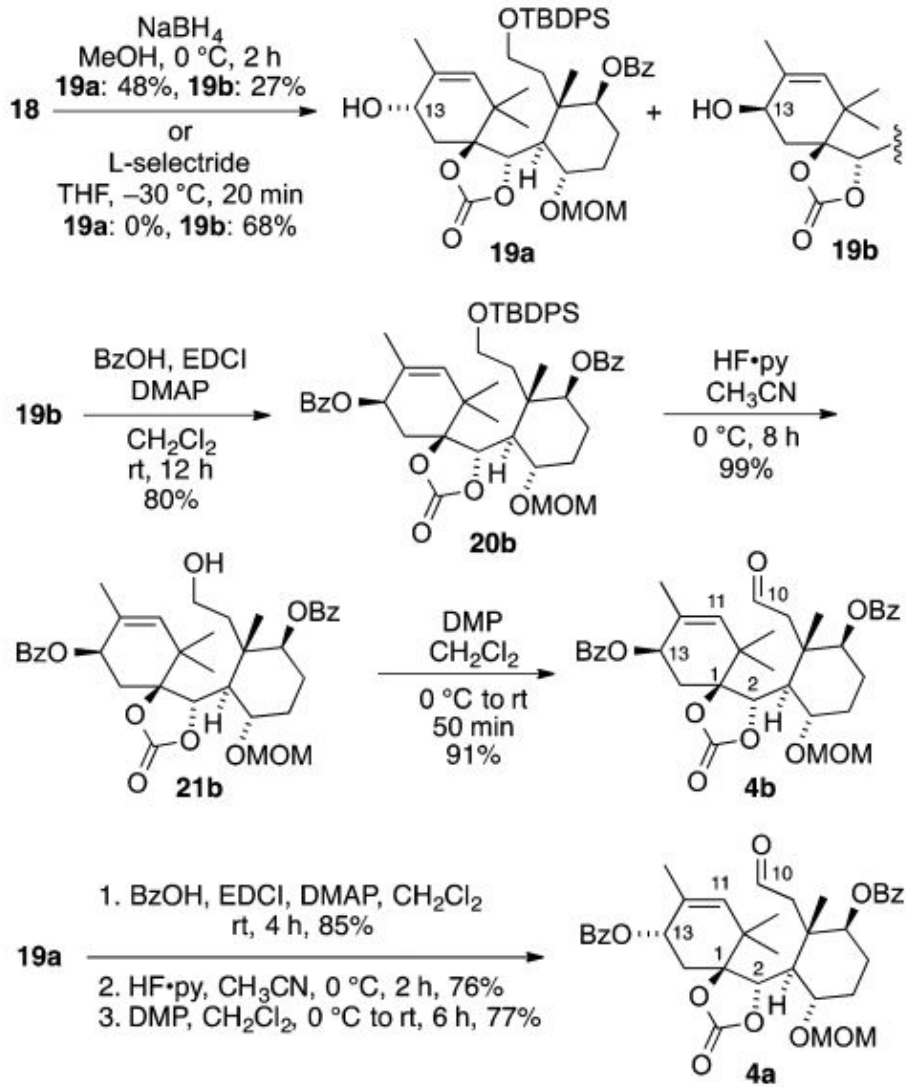
Synthesis of the C Ring of Paclitaxel



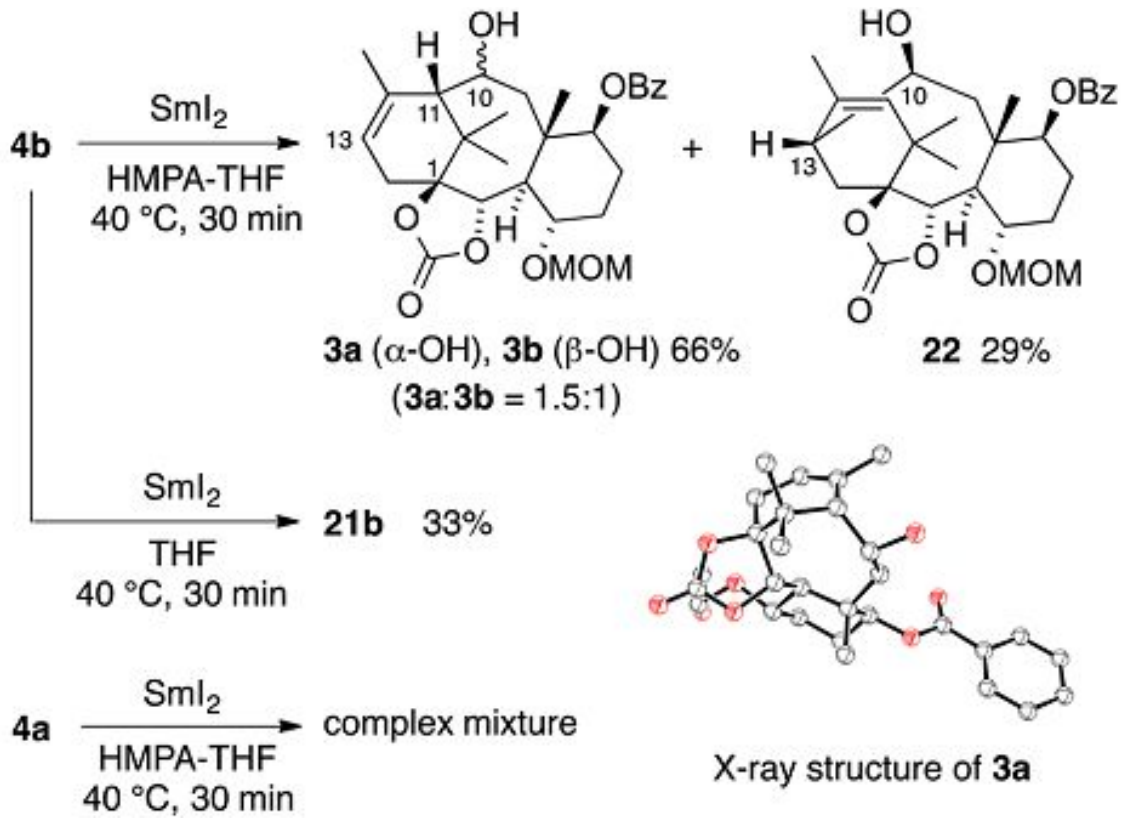
Preparation of the A–C Rings of Paclitaxel



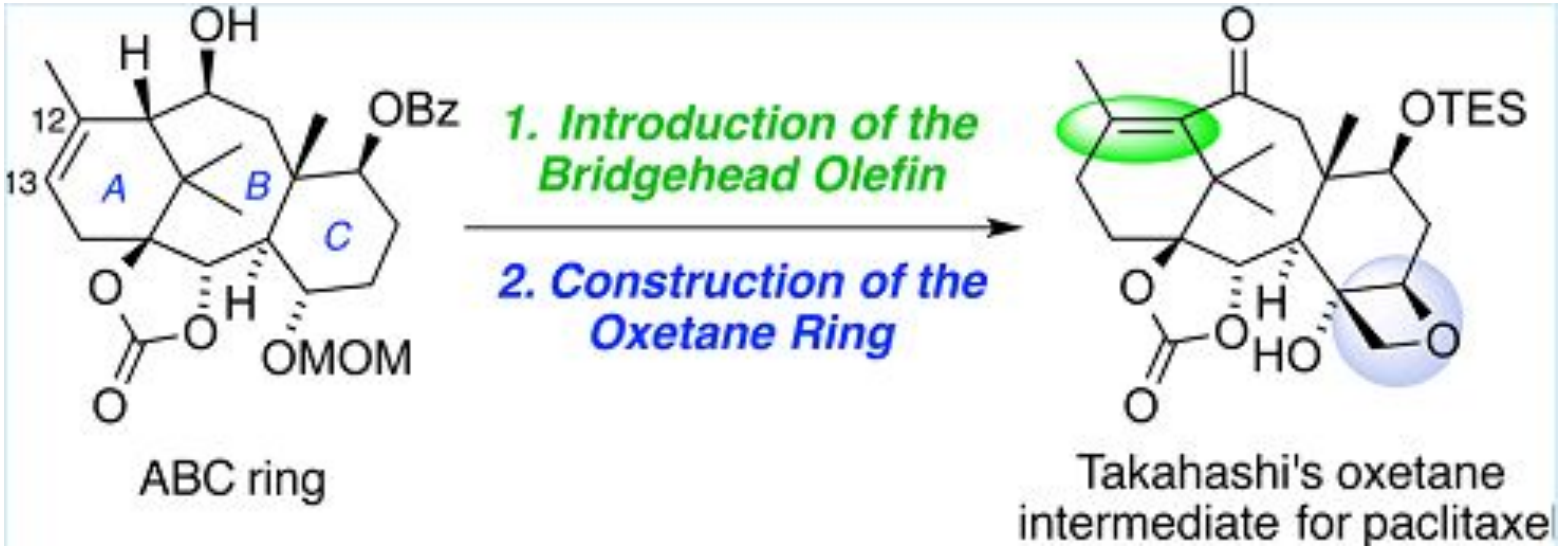
Preparation of the ABC Precursor 4



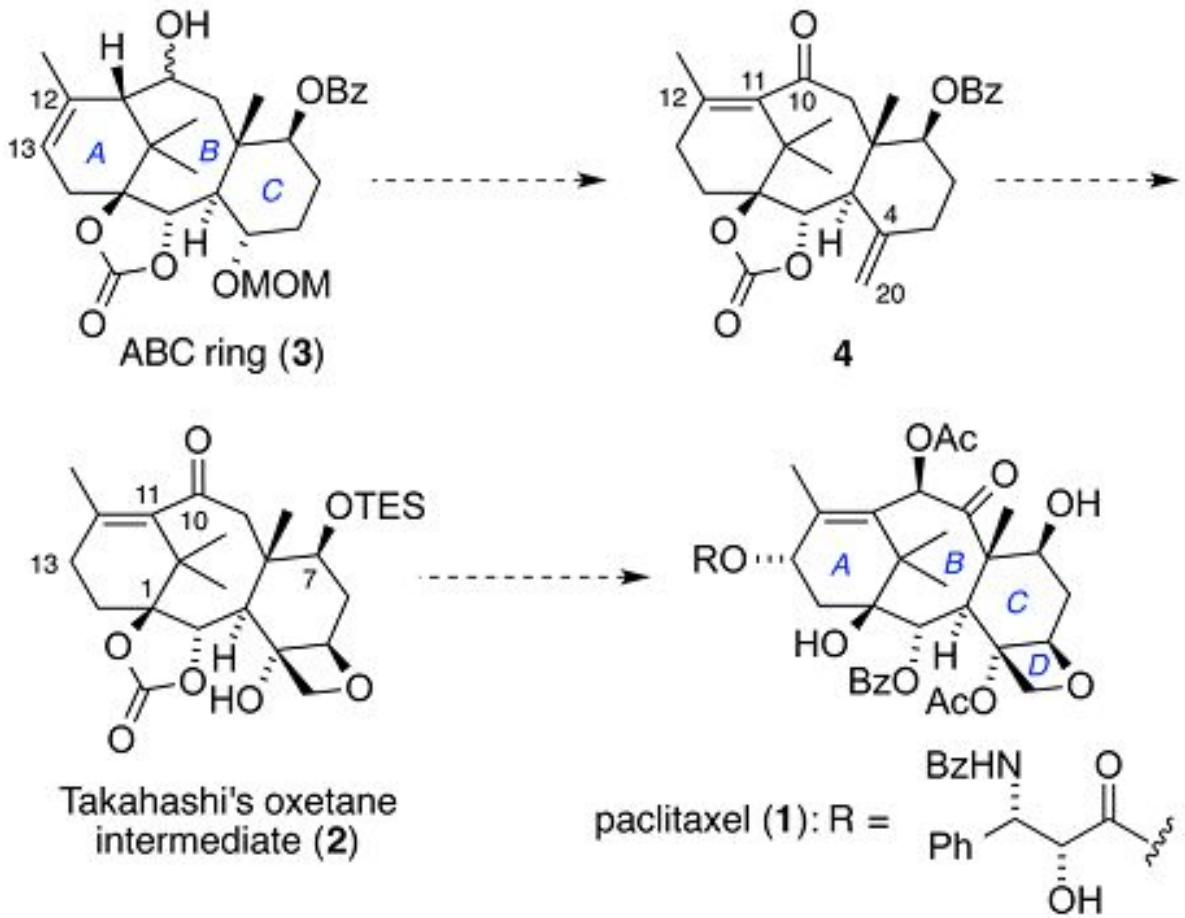
Construction of ABC Ring of Paclitaxel 3



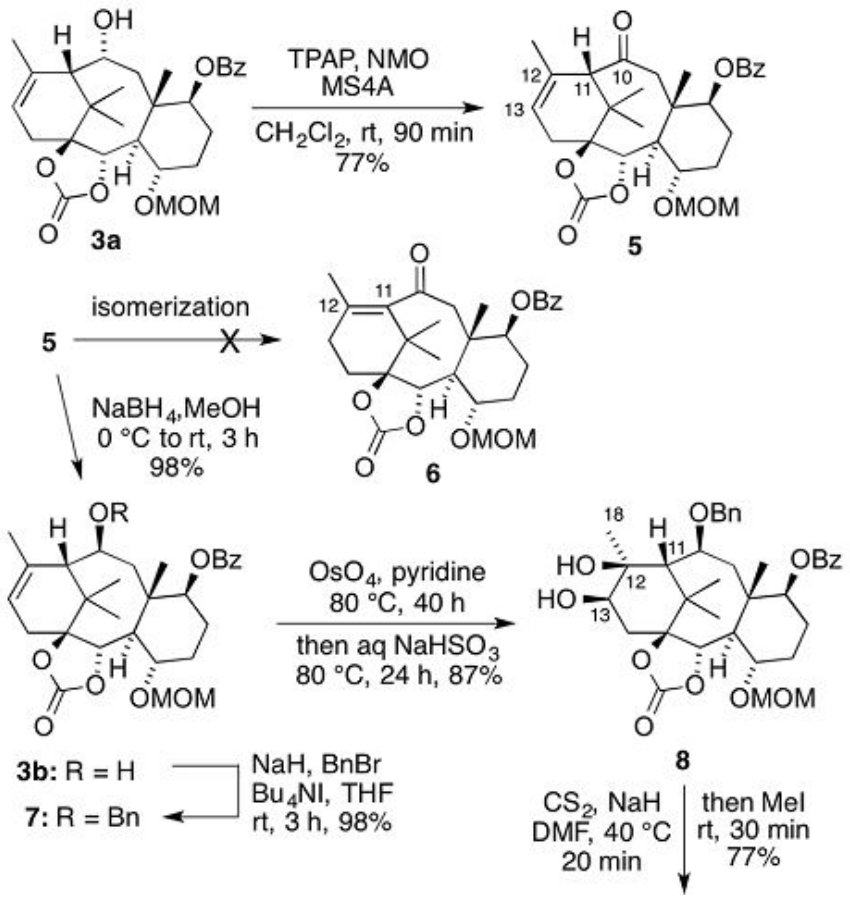
2. Construction of the ABCD Ring and Formal Synthesis

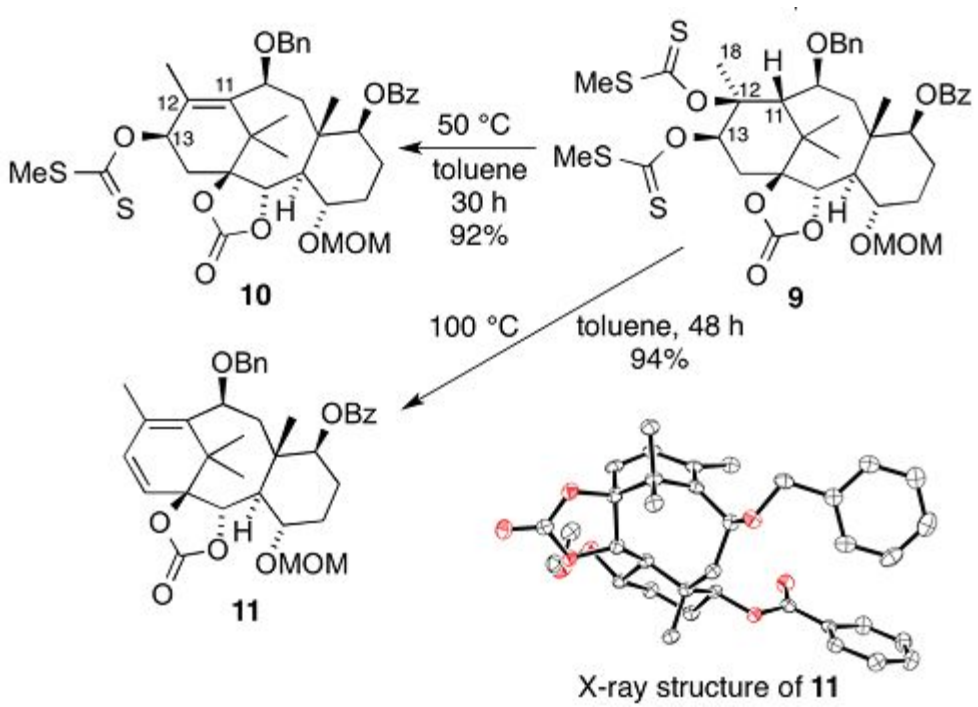


Synthetic plan for paclitaxel (1) from ABC ring (3)

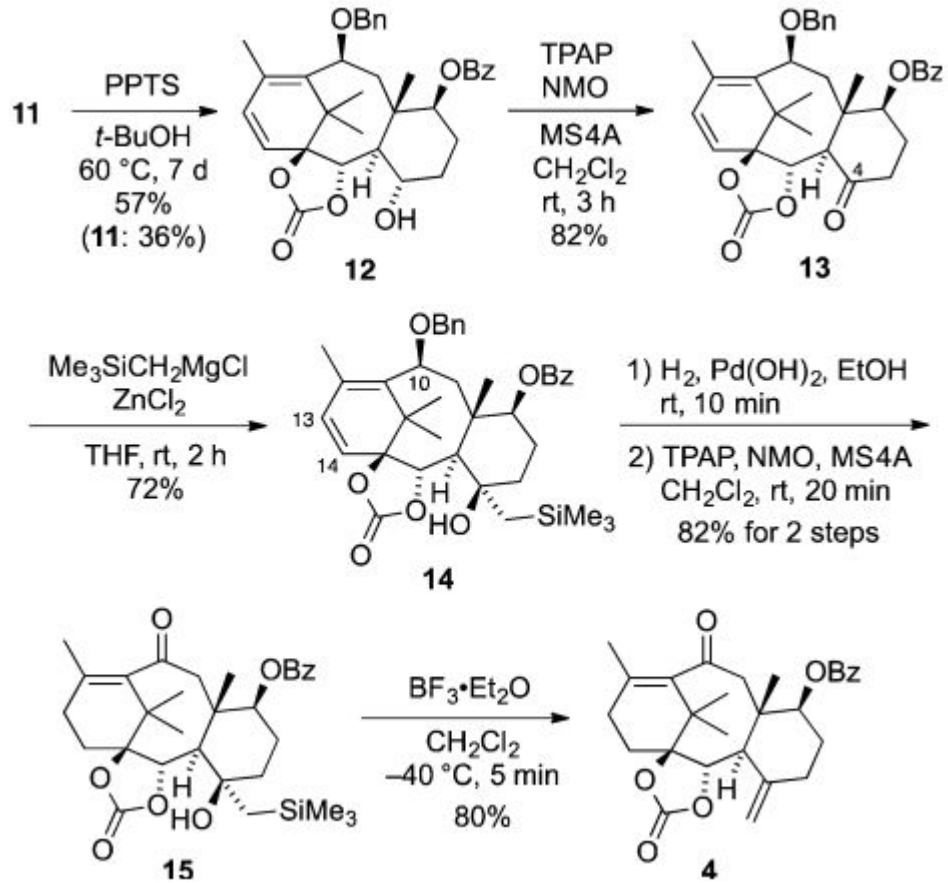


Construction of a Bridgehead Olefin by Chugaev Reaction

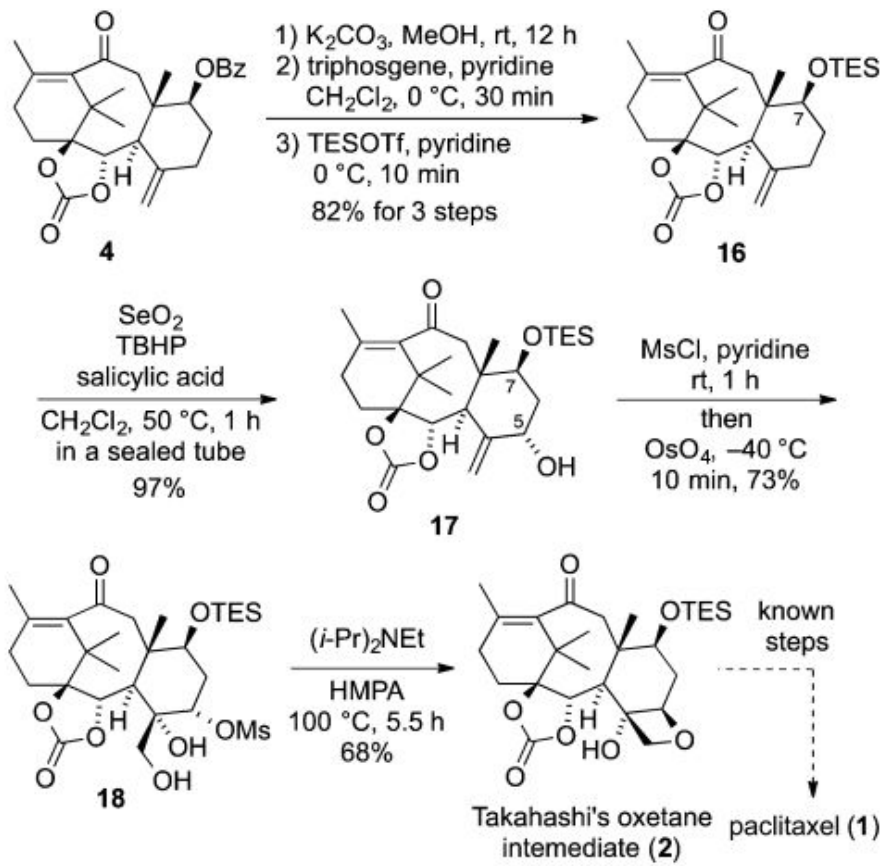




Synthesis of Taxoid 4



Synthesis of Takahashi's Oxetane Intermediate



3. Total synthesis of Taxol (baccatinIII) by Takashi

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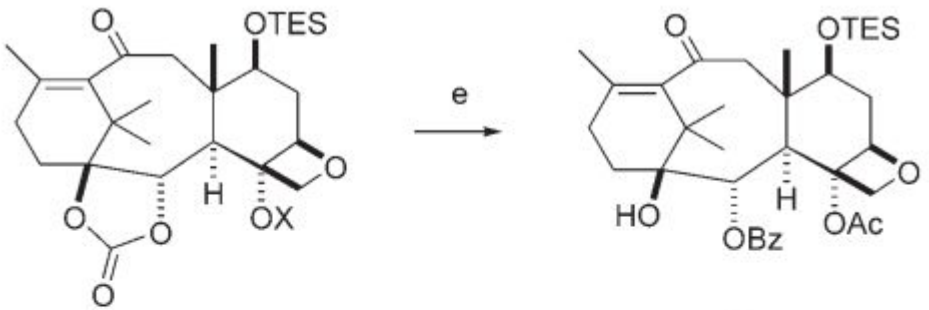
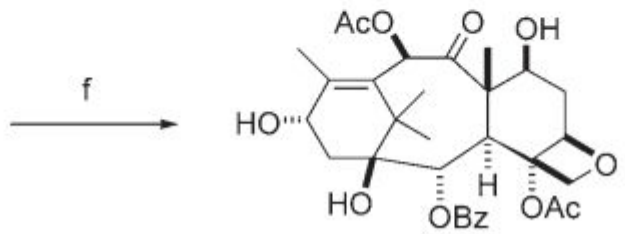
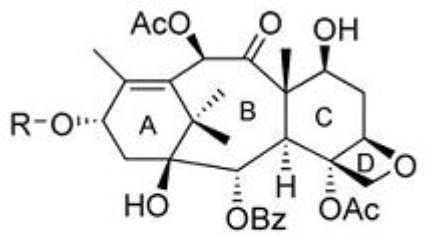
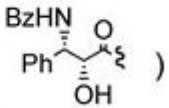


d) Ac_2O, DMAP, CH_2Cl_2 (70%); e) PhLi, THF, −78 °C (70%); f)[10] 1) *t*BuOK, $(PhSeO)_2O$, THF, −78→0 °C; 2) *t*BuOK, THF, −78 °C (90%), 3) Ac_2O, DMAP, pyridine (50%), 4) PCC, celite, NaOAc, benzene, 85 °C; 5) $NaBH_4$, MeOH (80%); 6) HF·pyridine, THF (80%). TES = triethylsilyl, HMPA = hexamethylphosphoric triamide, PCC = pyridinium chlorochromate. Bz = benzoyl.



(±)-baccatin III (**2**)

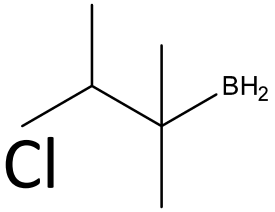


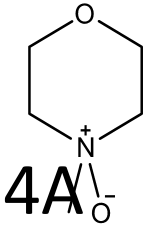
taxol (**1**): (R = 

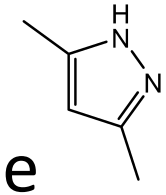
)

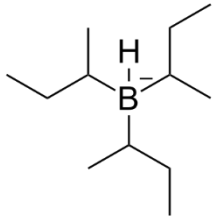
baccatin III (**2**): (R = H)

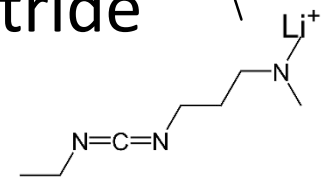
Abbreviation

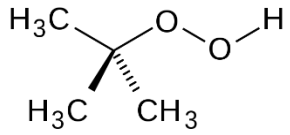
- Thexylborane 

- TBDPSCl $^{t}BuPh_2SiCl$
- TPAP Pr_4NRuO_4
- NMO 

- MS4A мол.сита 4A
- 3,5-DMP 

- L-selectride 

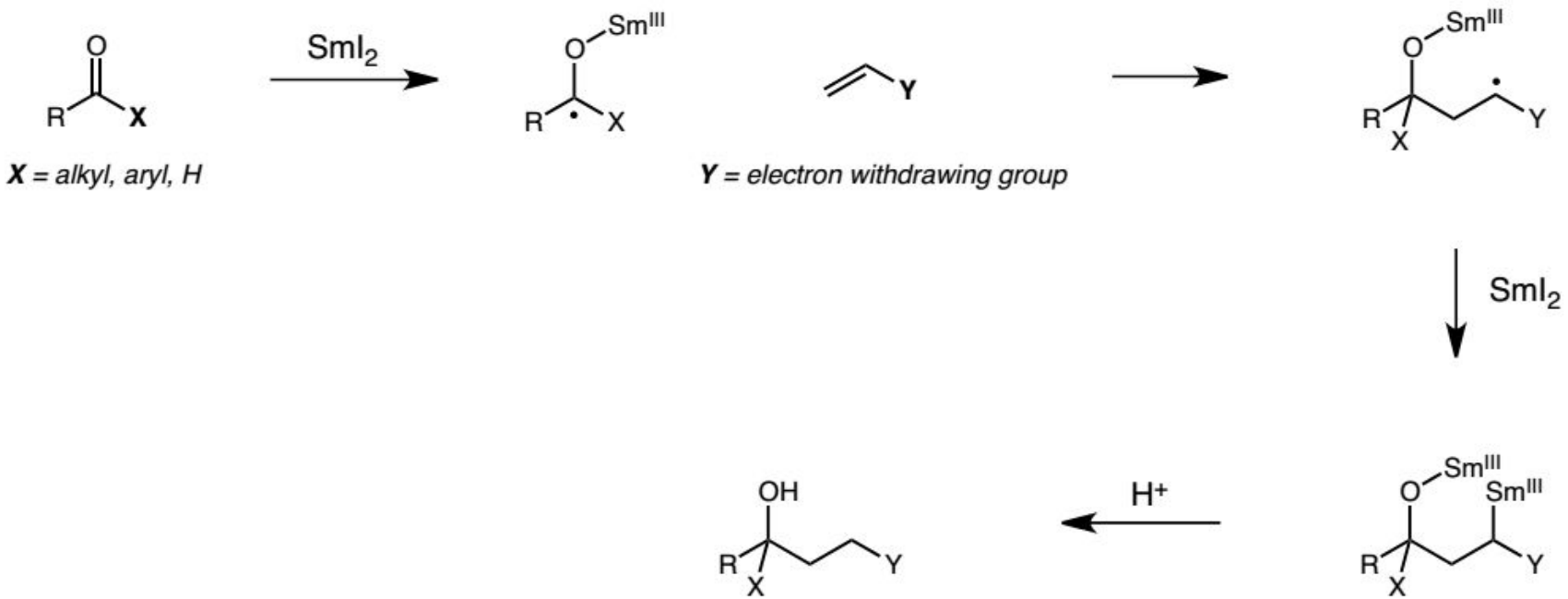
- EDCl 

- TBHP 

Carbon-Carbon Bond-forming Reactions Using SmI_2

■ Carbonyl-alkene coupling

Traditional mechanism

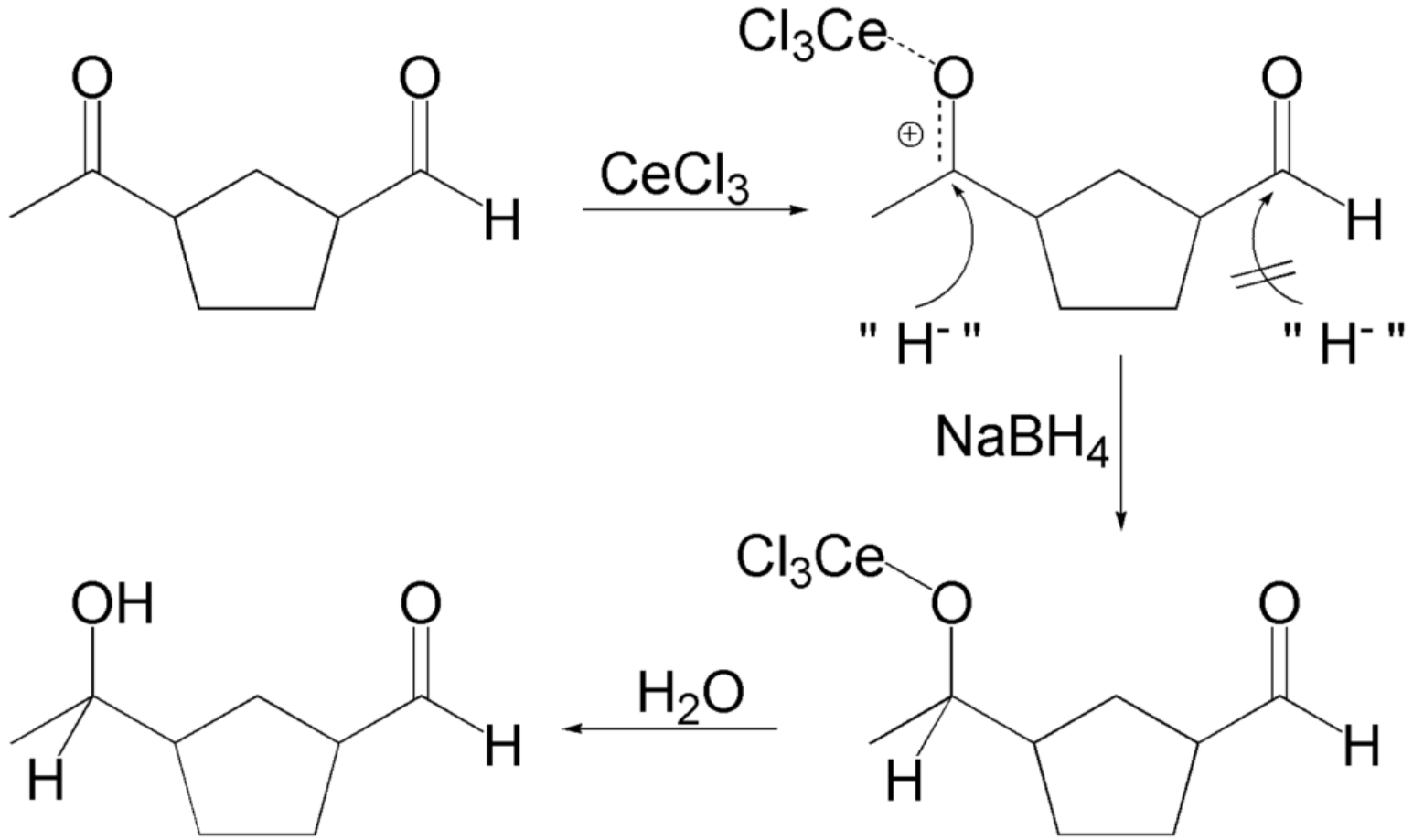


***X** = alkyl, aryl, H*

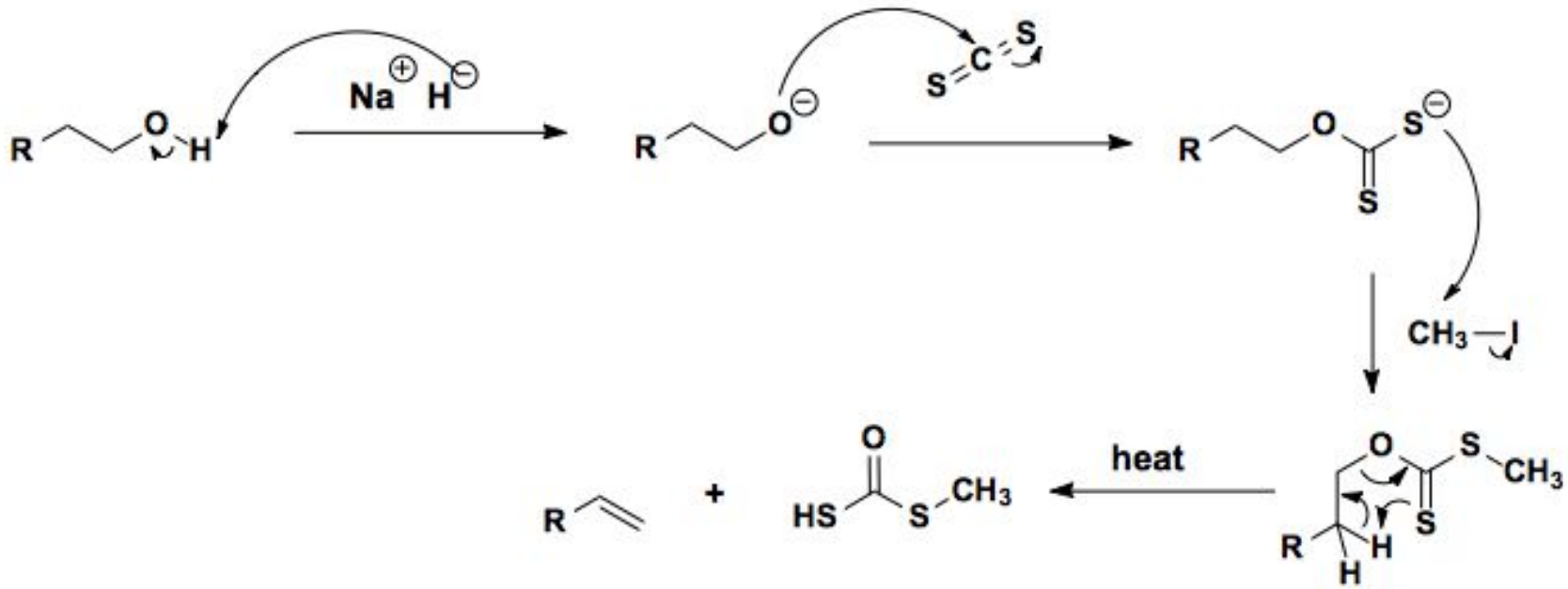
***Y** = electron withdrawing group*

■ Intramolecular carbonyl-alkene couplings display a greater degree of tolerance in alkene components

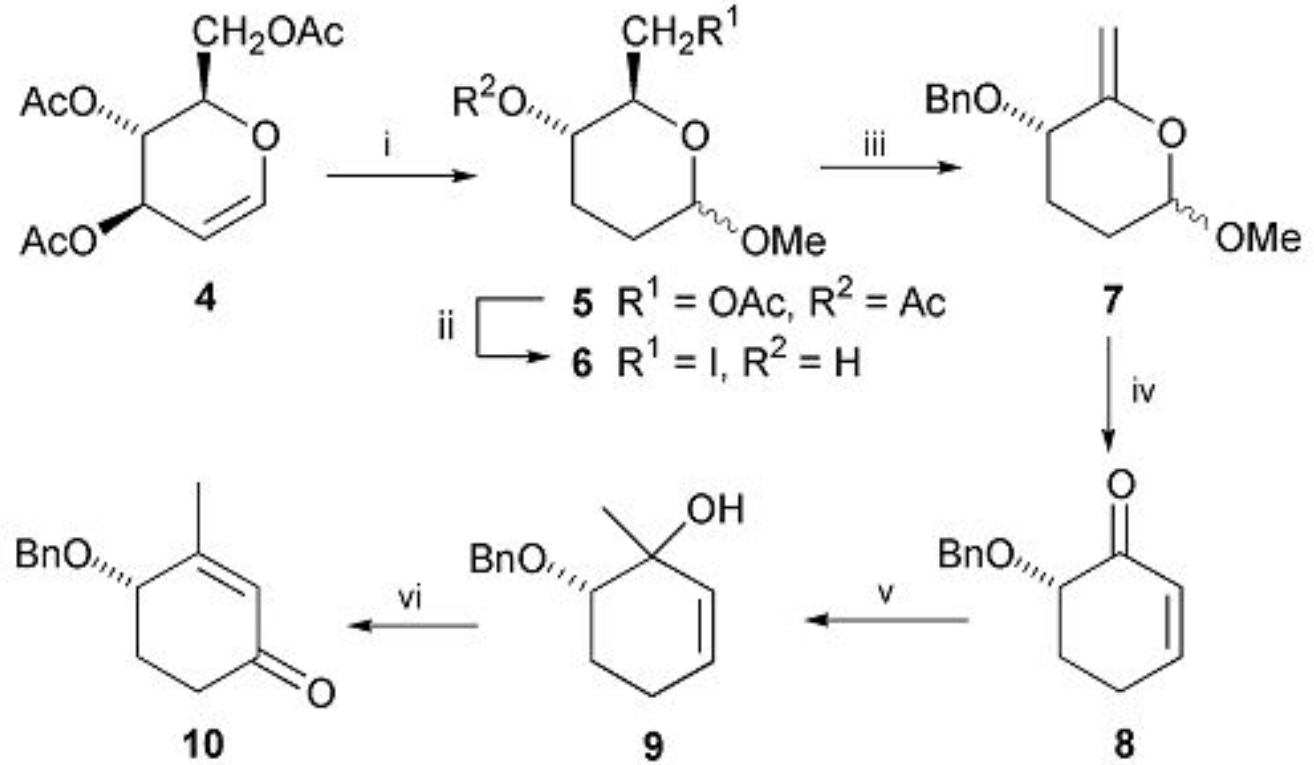
Luche reduction mechanism



Chugaev reaction mechanism



Preparation of 7 from tri-O-acetyl-D-glucal



Scheme 1 Bn = $-CH_2Ph$. *Reagents and conditions*: i, MeOH, $BF_3{\cdot}OEt_2$, PhH, 0 °C, then H_2, 10% Pd-C, EtOAc, rt; ii, MeONa, MeOH, 0 °C, then I_2, Ph_3P, imidazole, THF, rt; iii, NaH, DMF, 0 °C, then BnBr, *n*-Bu_4NI, DMF, 0 °C; iv, $Hg(OCOCF_3)_2$ (5 mol%), acetone–H_2O (2:1), 0 °C, then MsCl, Et_3N, CH_2Cl_2, 0 °C; v, MeLi, Et_2O, −78 °C; vi, PCC, molecular sieves 4 Å (powder), CH_2Cl_2, rt.

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