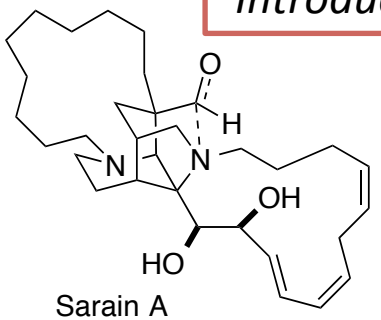
Formal Synthesis of Sarain A: Intramolecular Cycloaddition of an Eight-Membered Cyclic Nitrone to Construct the 2-Azabicyclo-[3.3.1]nonane Framework

Takuya Higo, Tomoya Ukegawa, Satoshi Yokoshima,* and Tohru Fukuyama
Graduate School of Pharmaceutical Sciences, Nagoya University, Japan
Angew. Chem. Int. Ed. DOI: 10.1002/anie.201501633

Presented by Zhiqiang Liu , The Liu Research Group , Boston College

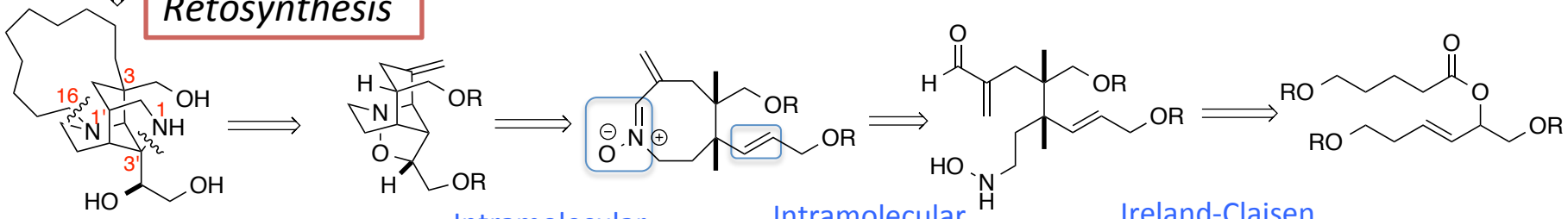
Introduction



Sarain A

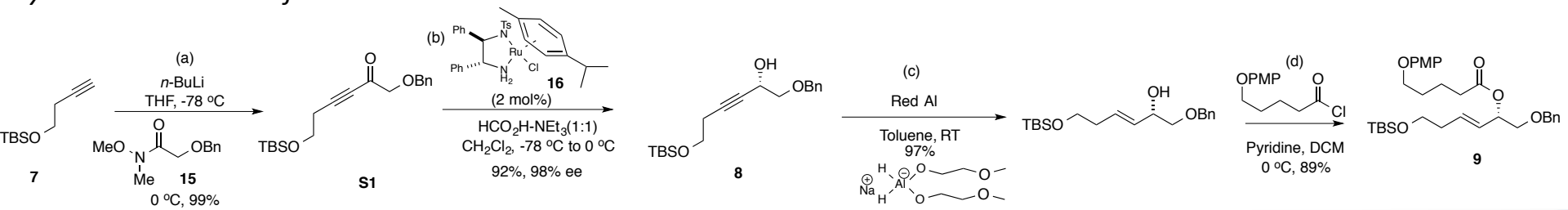
- An alkaloid, firstly isolated in 1986 from the sponge *Reniera saria*.
- Pentacyclic compound with 2,8-di-azatriicyclo[5.4.0.0]undecane core.
- Seven stereogenic centers, intramolecular proximity interaction, sensitive to pH and micro-environment.
- Overman et al did the first and only total synthesis.
  [*J. Am. Chem. Soc.*, **2007**, *129* (39), pp 11987–12002]

Retosynthesis

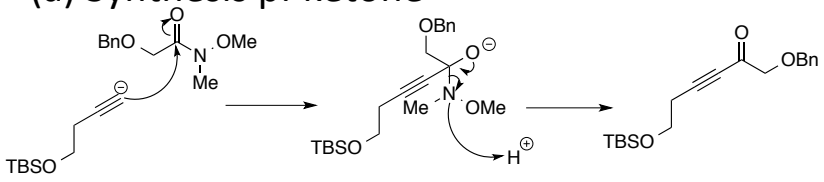


2 (Overman's **124**) **3** Intramolecular Cycloaddition **4** Intramolecular Condensation **5** Ireland-Claisen Rearrangement **6**

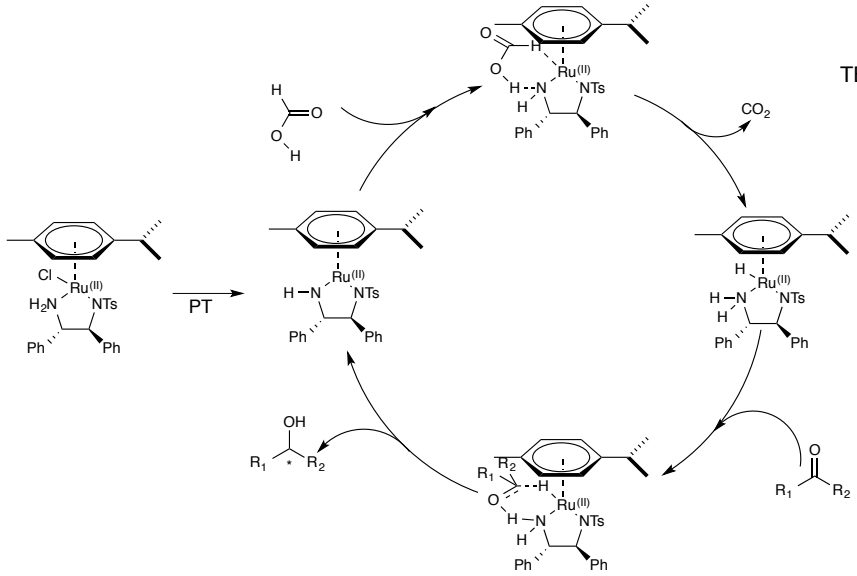
Synthesis: Precursor of intramolecular addition



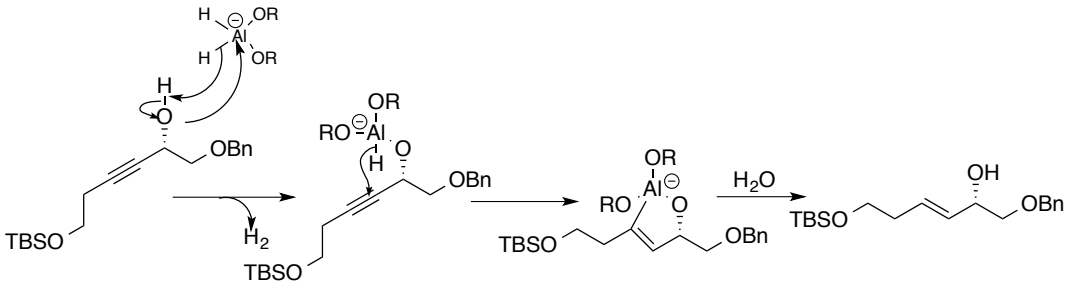
(a) Synthesis pf ketone



(b) Noyori asymmetric reduction of Ketone

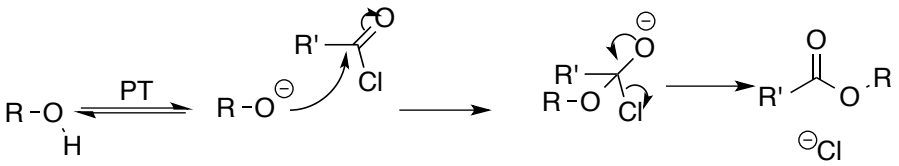


(c) Reduction of propargyl alcohol



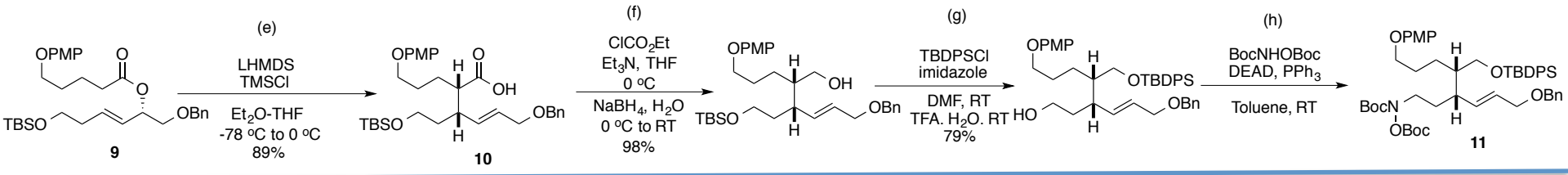
J. Org. Chem. **2003**, *68*, 9274.

(d) Acylation

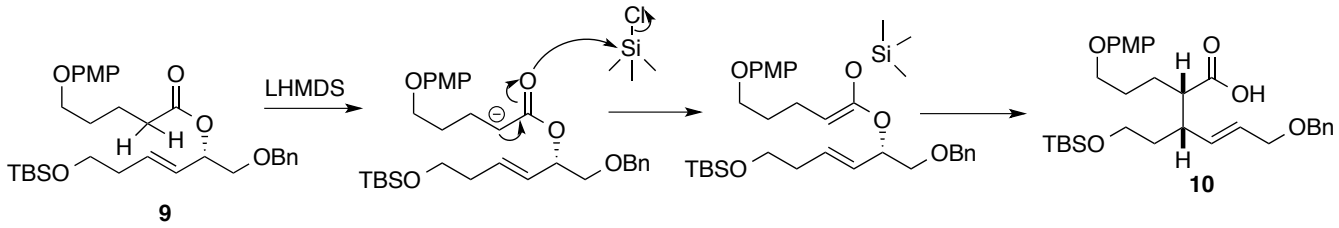


J. Am. Chem. Soc., **1995**, *117* (28), pp 7562–7563

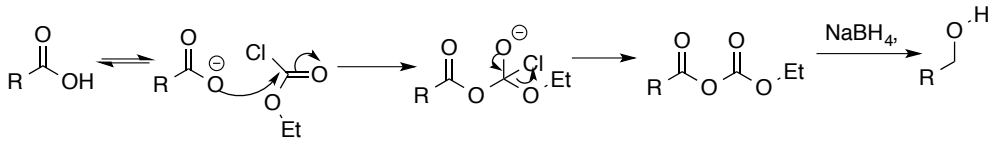
Synthesis: Precursor of intramolecular addition



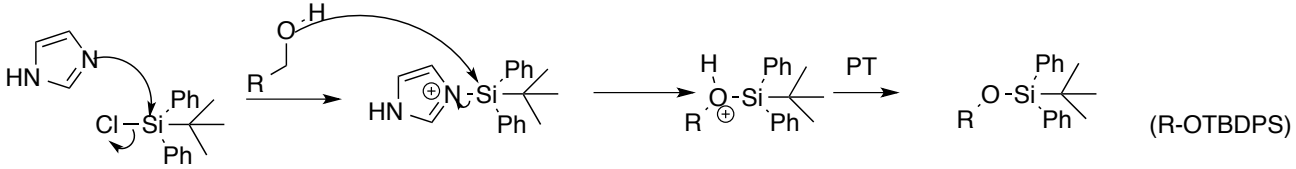
(e) Ireland-Claisen rearrangement



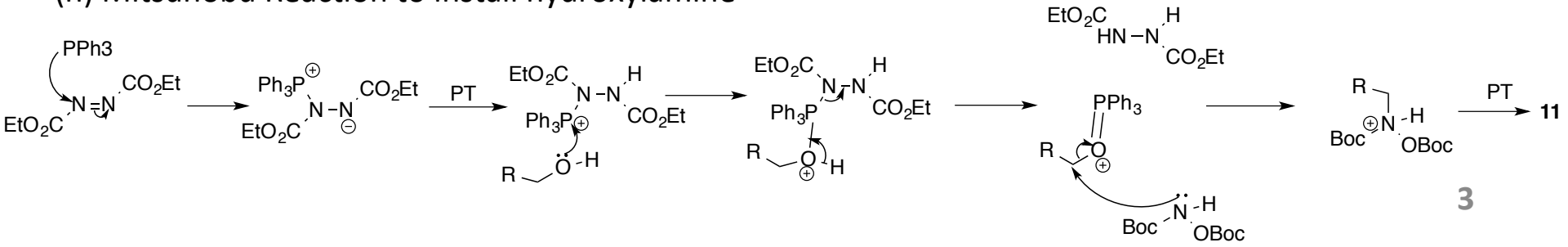
(f) Reduction of carboxylic acid



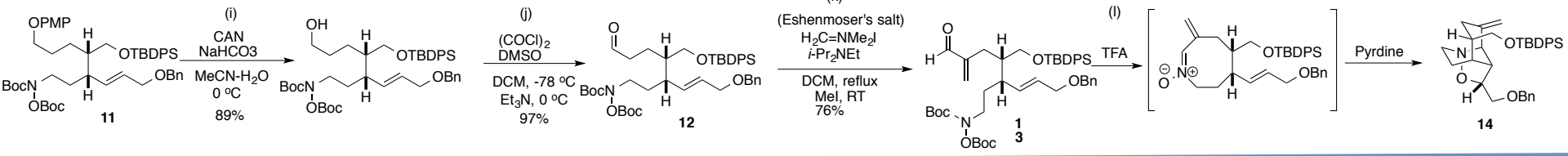
(g) Protection of OH with TBDPSCl



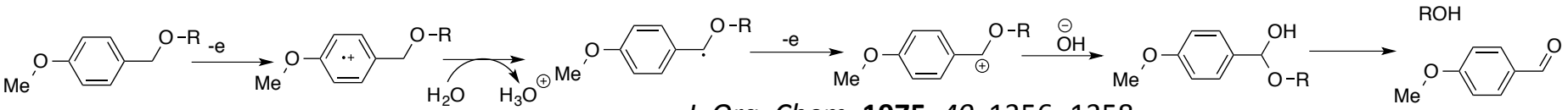
(h) Mitsunobu Reaction to install hydroxylamine



Synthesis: intramolecular addition

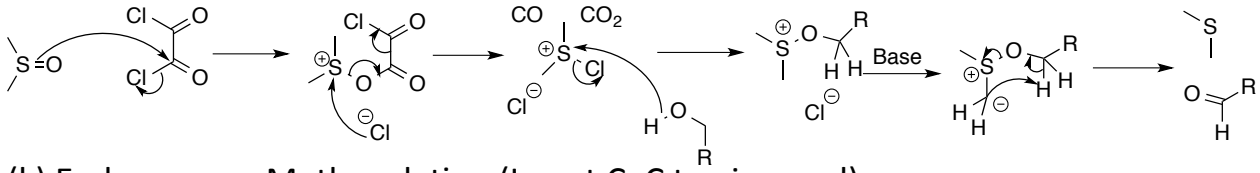


(i) Cleavage of PMP with CAN (Deprotection of PMP to alcohol)

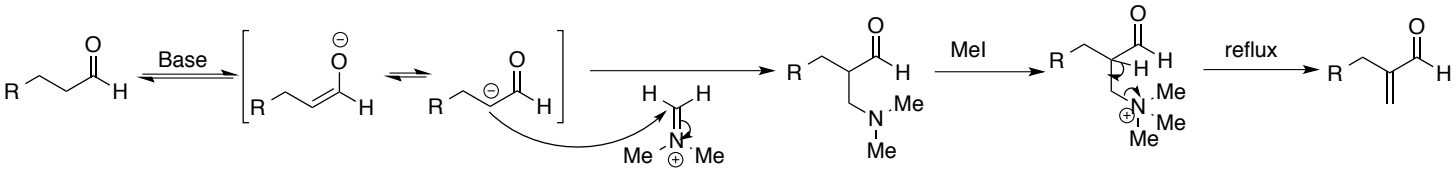


J. Org. Chem. **1975**, *40*, 1356- 1358.

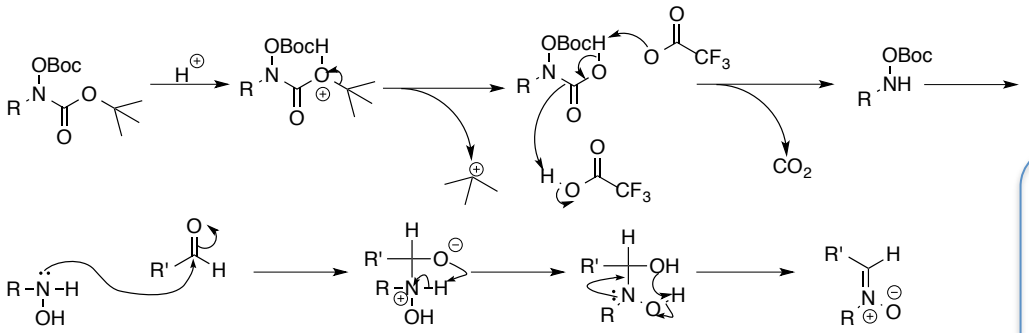
(j) Swern Oxidation to give aldehyde



(k) Eschenmoser Methenylation (Insert C=C to give enal)

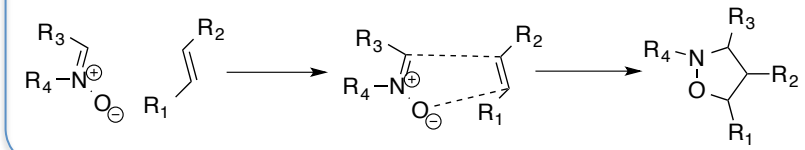


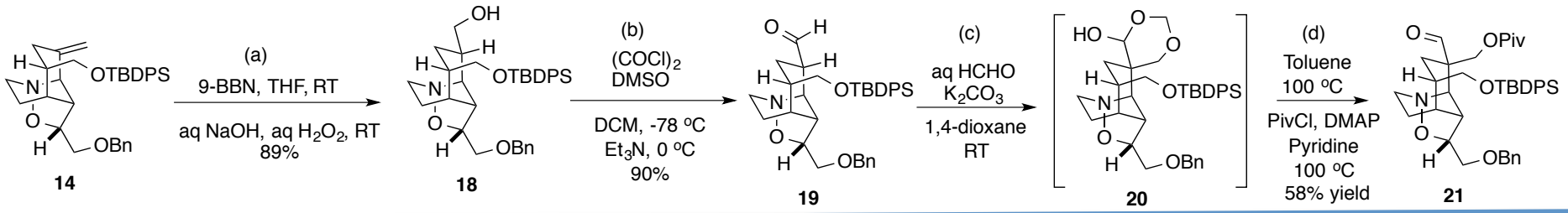
(l) Deprotection of hydroxylamine and condensation with aldehyde to produce cyclic nitrone



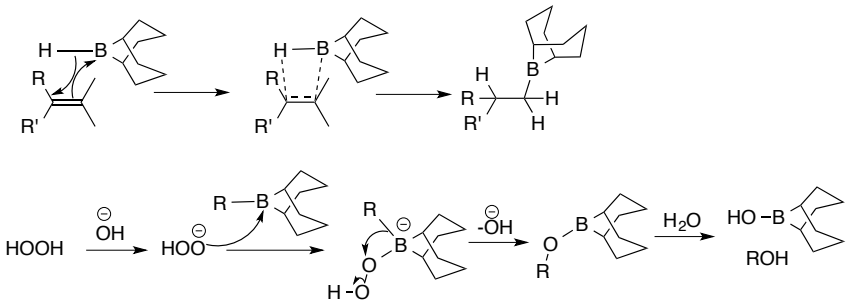
Boc group on O can be deprotected similarly.

Nitrone-olefin 3+2 cycloaddition



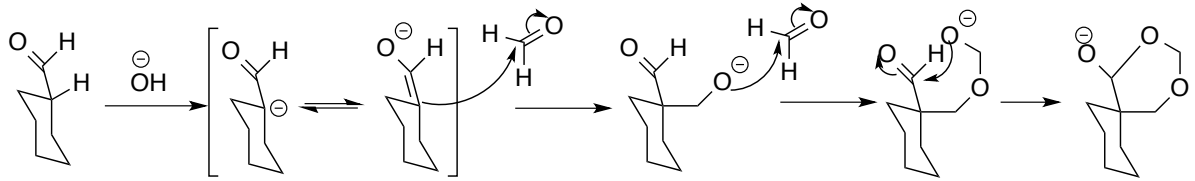


(a) Hydroboration and Oxidation

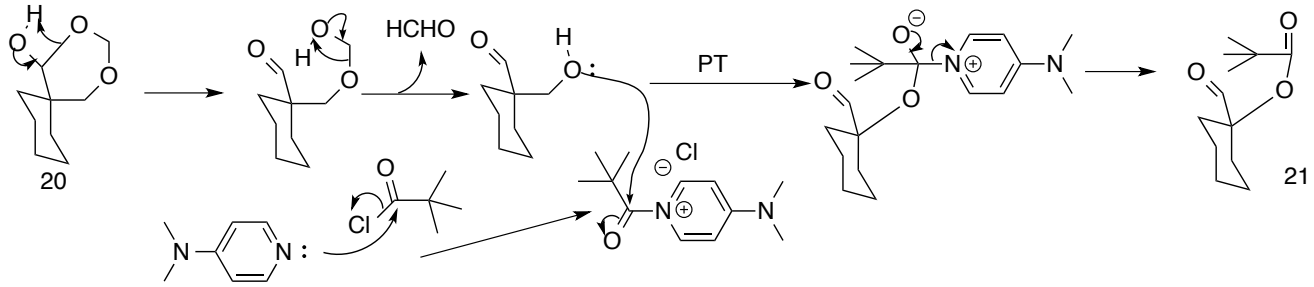


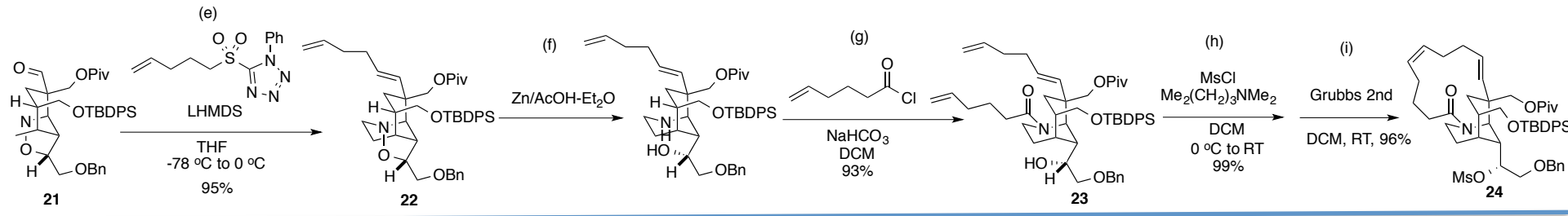
(b) Swern Oxidation to produce aldehyde again

(c) Aldol reaction—Deprotection-Piv protection

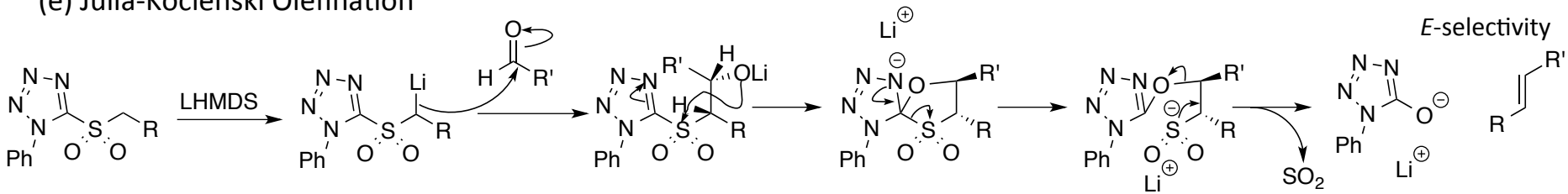


(d) Deprotection of aldehyde and protection of alcohol

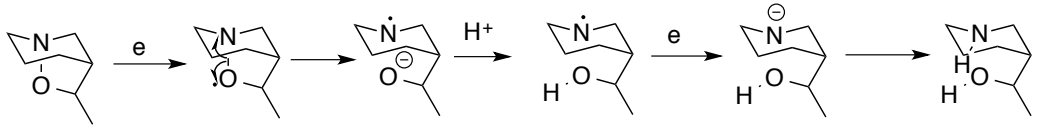




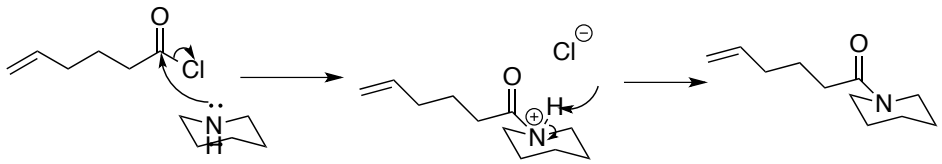
(e) Julia-Kocienski Olefination



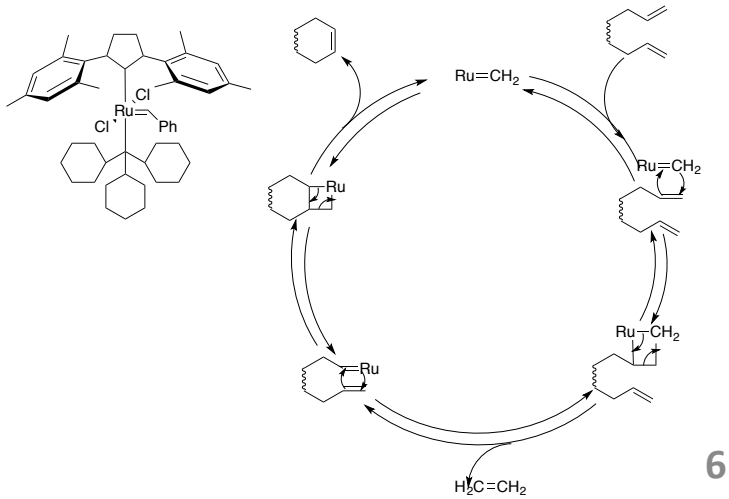
(f) Zinc reduction to cleavage N-O bond



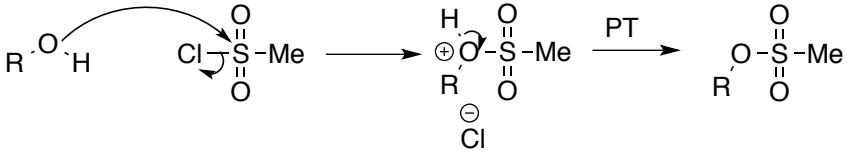
(g) Acylation of secondary amine to insert another alkene

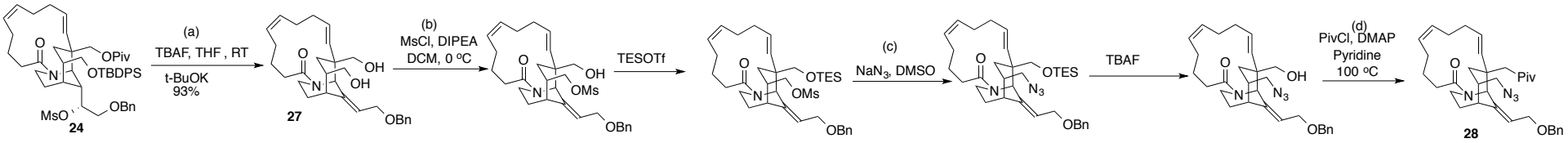


(i) Ring closing metathesis to build 13 membered ring



(h) Protection of OH with MS group



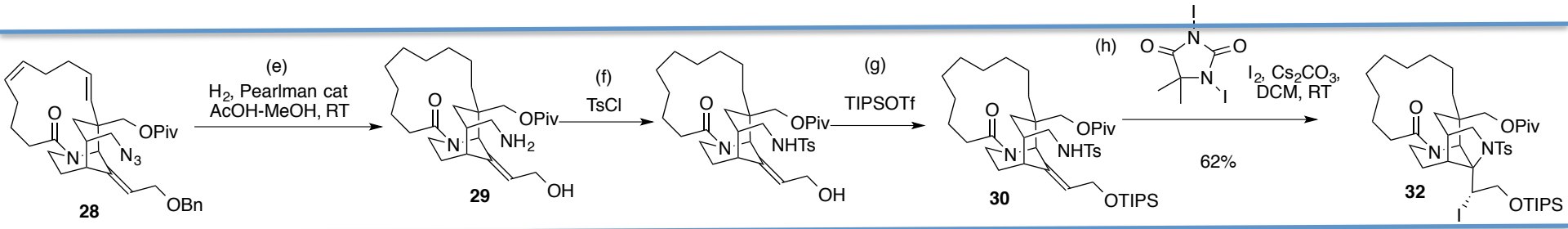


(a) Removal of TBDPS, and elimination of mesyloxy group to form C=C bond, and also cleave the pivaloyl ester

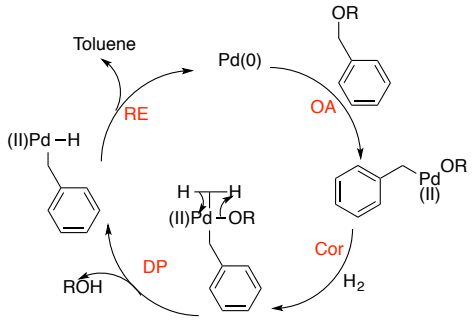
(b) Selective protection of alcohol: firstly added: 1. 0 eq of MsCl; secondly added 2.0 eq of TESOTf

(c) introduce azide group: Substitution of OMs with azide (SN2), and removal of TES group.

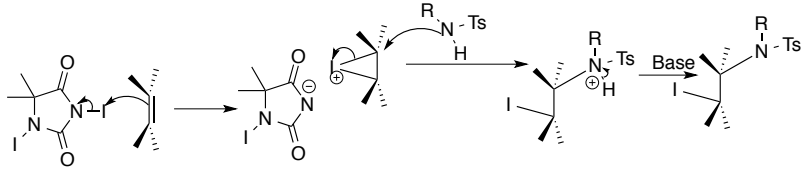
(d) Re-protect of OH with Piv.



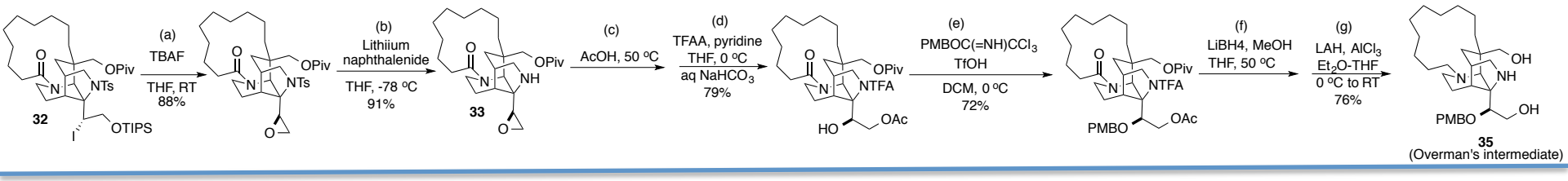
(e) Pd-catalyzed hydrogenolysis and reduction of azide



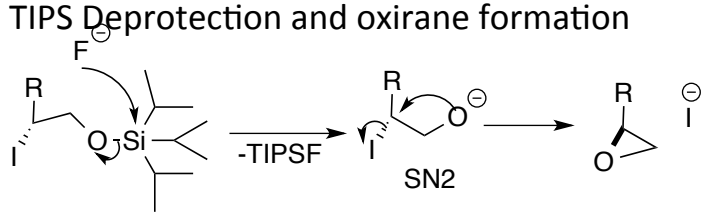
(f) Iodine addition and cyclization



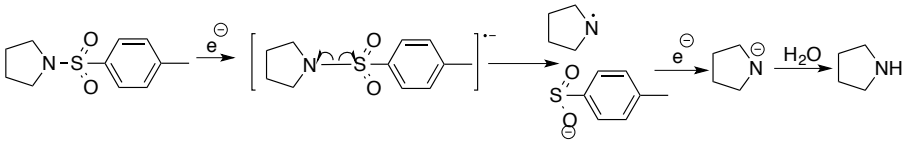
Conversion into Overman's intermediate



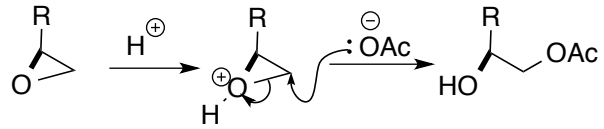
(a) TIPS Deprotection and oxirane formation



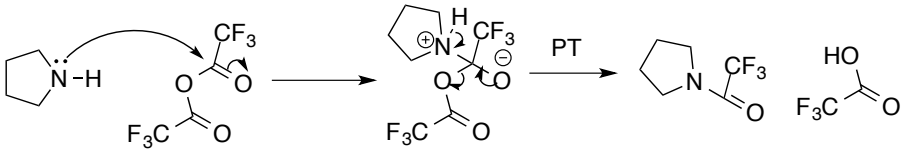
(b) Reductive desulfonylation to remove tosyl group



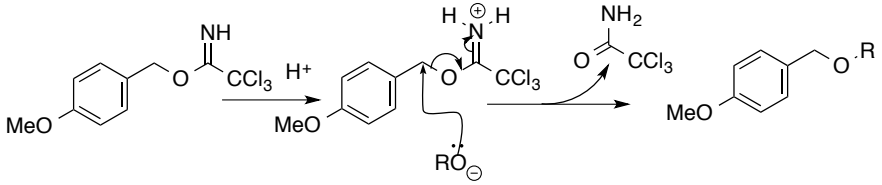
(c) Opening of epoxide with acid



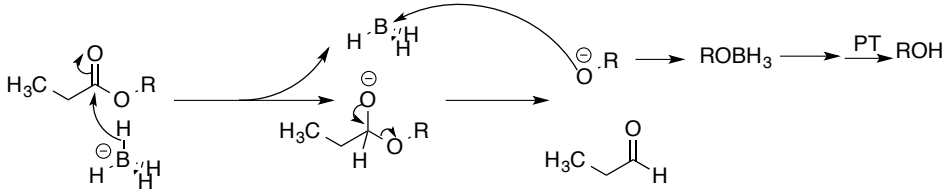
(d) Amidation (protection of NH)



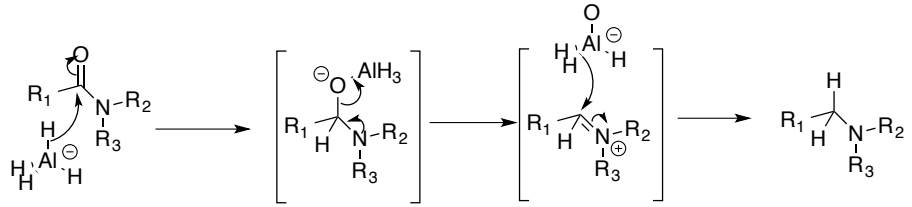
(e) Protection of Hydroxyl with PMB



(f) Reductive cleavage of acyl groups



(g) Reduction of amide with LAH



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