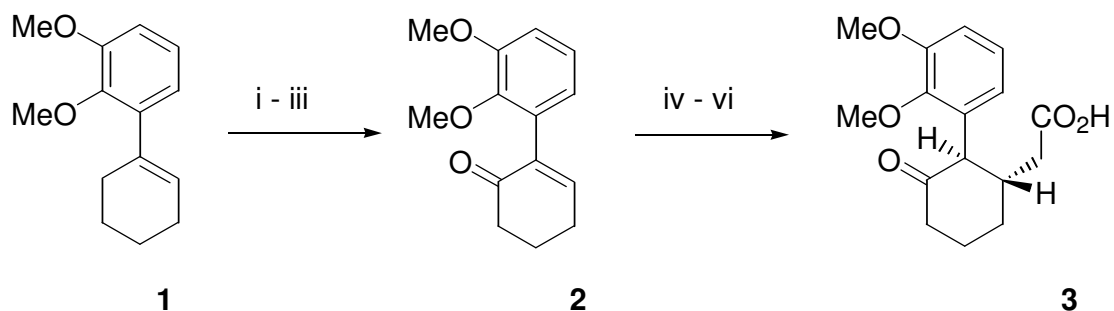


Ginsberg's synthesis of (+/-) Morphine (1953)

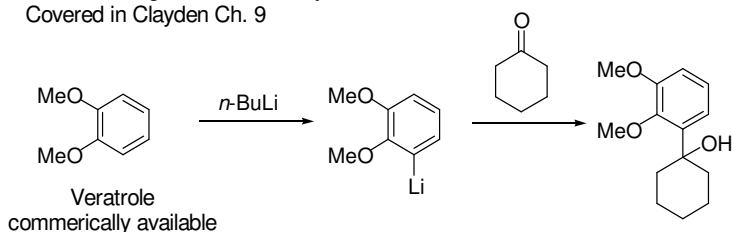
Sequence 1



• Preparation of starting material

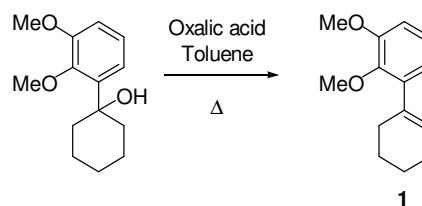
Directed-lithiation followed by carbon-carbon bond formation.

Chem4/5: Organometallics in synthesis
Covered in Clayden Ch. 9



Elimination (dehydration)

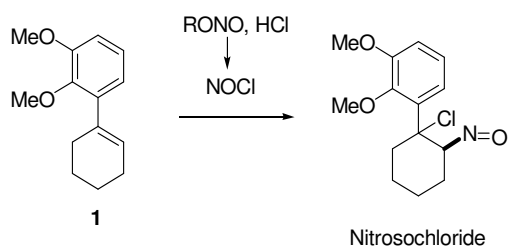
Chem 2: Stereochem and reaction mech.
Covered in Clayden Ch. 19



• Steps i-iii

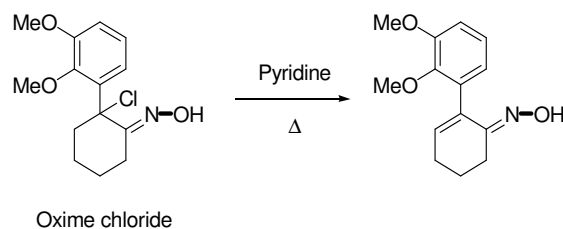
i. Allylic oxidation using NOCl

Nitroso group discussed in Clayden Ch. 21, pp538-540
This reaction discussed in March (5th ed.) pp1045-1046



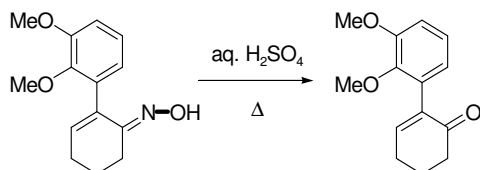
ii. Elimination

Chem2: Stereochem and reaction mech.
Nitroso group discussed in Clayden Ch. 9



iii. Oxime hydrolysis

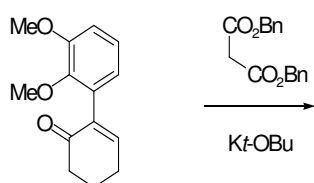
Chem1B: Chem of carbonyl group
Discussed in Clayden p351 and p539



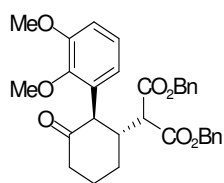
• Steps iv-vi

iv. Michael addition

Chem2: Carbonyl chemistry
Clayden Ch. 29

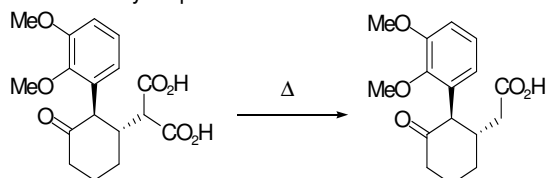


v. Hydrogenolysis

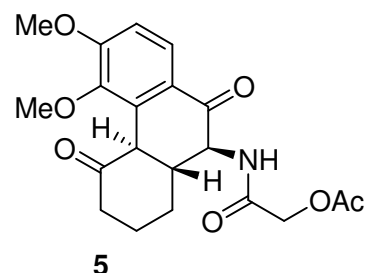
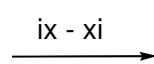
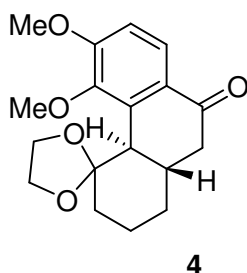
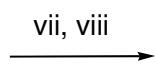
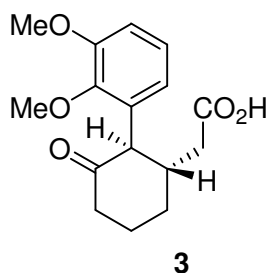


vi. Decarboxylation

Chem2: Carbonyl chemistry
Clayden p678



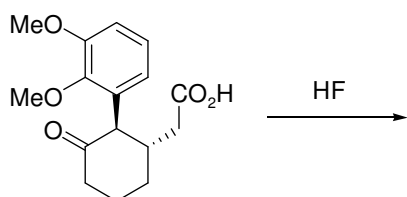
Sequence 2



• Steps vii-xi

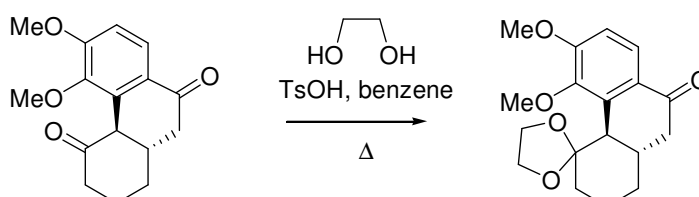
vii. Cyclisation: Friedel-Crafts acylation

Chem2: Aromatic Chemistry
Clayden Ch. 22

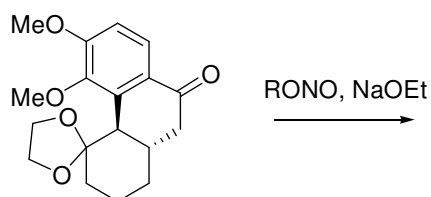


viii. Ketal protection

Chem1B: Chemistry of the carbonyl group
Clayden pp342-348

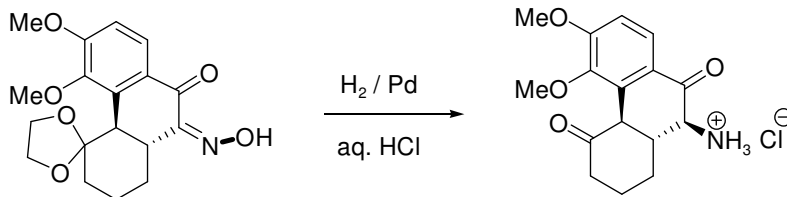


ix. Amination of enolate, cf step i



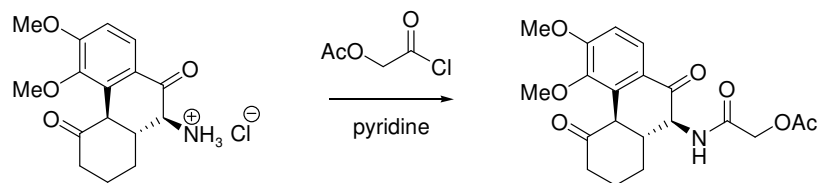
x. Oxime reduction with *in situ* ketal hydrolysis

March (5th Ed.) p1554 for redn. step

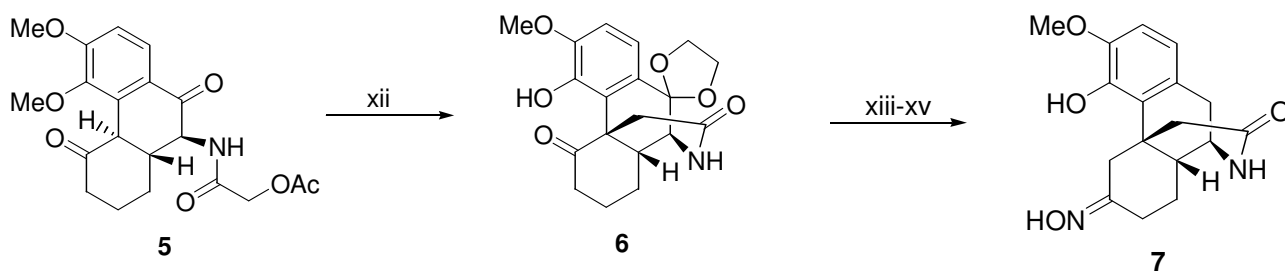


xi. Amine acylation

Chem1B: Functional group course
Clayden p284



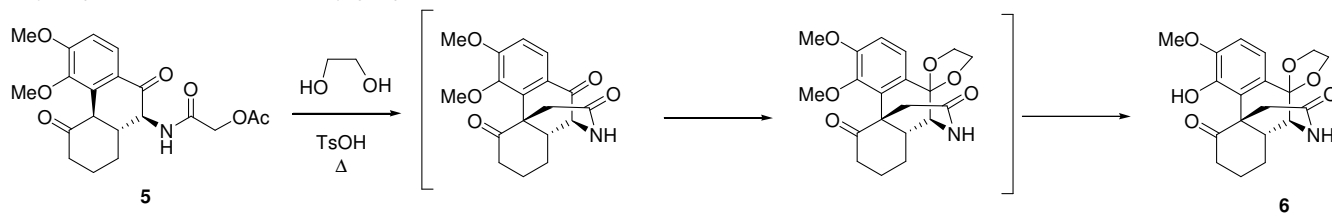
Sequence 3



• Steps xii-xiv

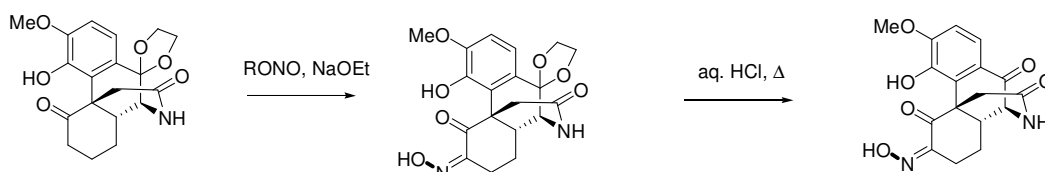
xii. Ketal protection (as in step viii), with intramolecular $\text{S}_{\text{N}}2$ cyclisation and demethylation (!!)

Chem1B: Chem of carbonyl compounds / Chem2: Stereochem and reaction mech.
Clayden p890 for $\text{S}_{\text{N}}2$ next to a carbonyl group

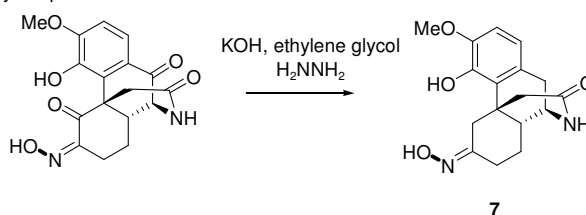


xiii. Amination (as in step ix)

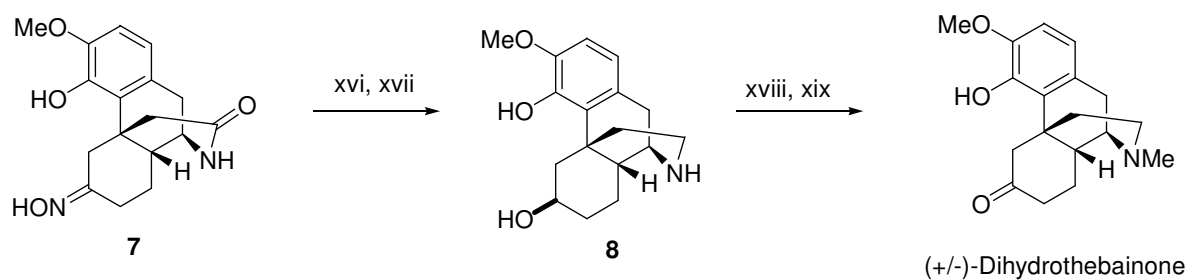
xiv. Ketal hydrolysis (as in step x)



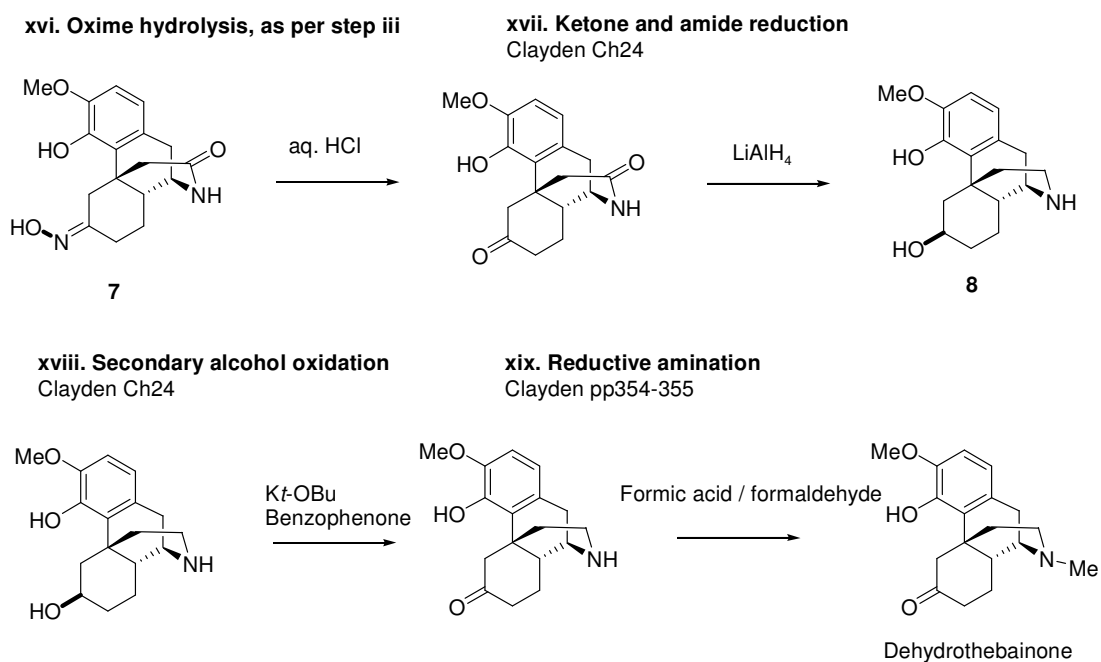
xv. Wolff-Kishner reduction Clayden p627



Sequence 4

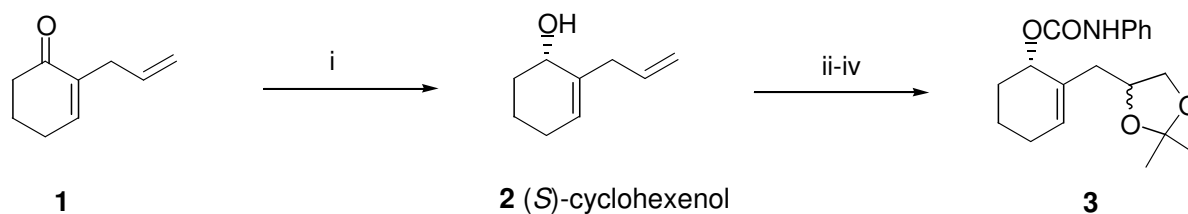


Steps xvi-xix



Overman's asymmetric synthesis of Morphine (1993)

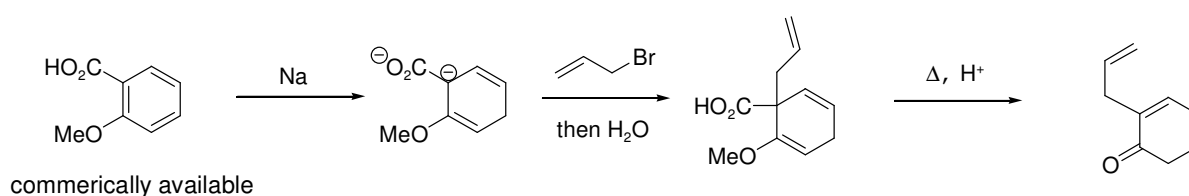
Sequence 1



• Preparation of starting material

One-pot Birch Reduction/alkylation/decarboxylation .

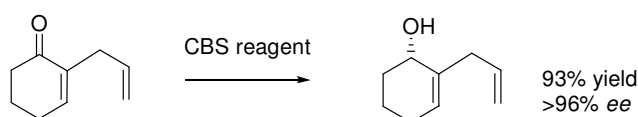
Birch red. covered in Clayden pp628-629



• Step i

Asymmetric Reduction.

Chem3: Asymmetric synthesis
Clayden p1233

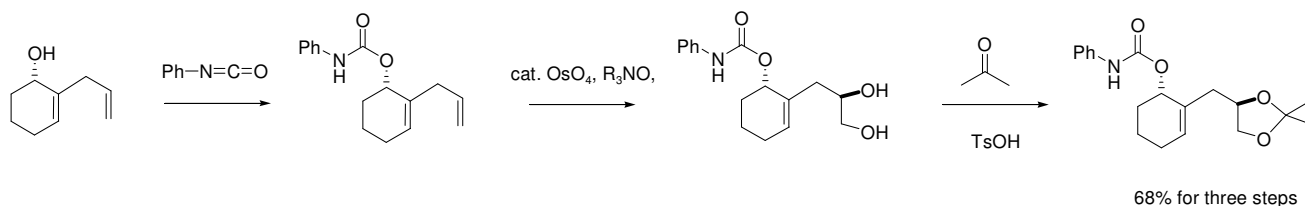


• Steps ii-iv

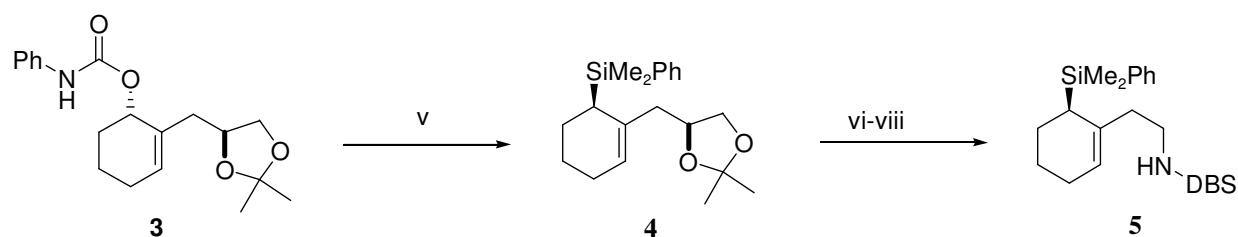
Carbamate formation
March (5th Ed.) pp1182-1183

Dihydroxylation
Chem3: Asymmetric synthesis
Clayden pp937-8

Ketal formation
cf Ginsberg's synthesis



• Sequence 2

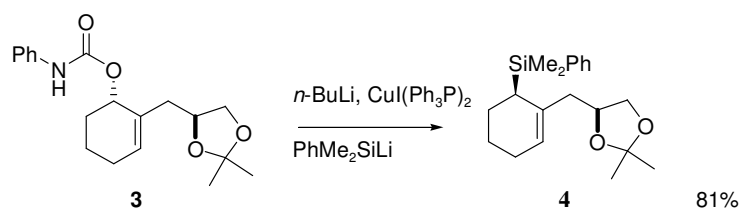


Step v

S_N2' displacement with silyl nucleophile

Chem2: Stereochem and reaction mech. for S_N2'

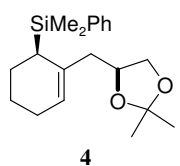
Clayden pp604-606



• Steps vi-viii

Ketal Hydrolysis

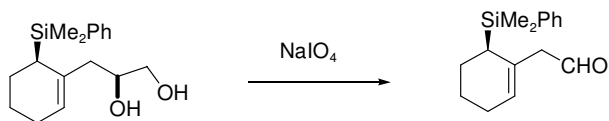
cf Ginsberg's synthesis



Diol Cleavage

Chem1: Functional group course

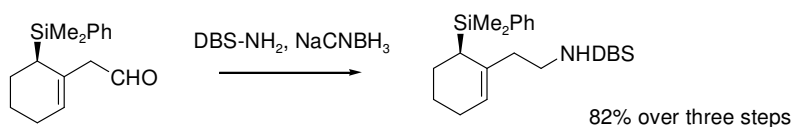
March 5th Ed. pp1519-1521



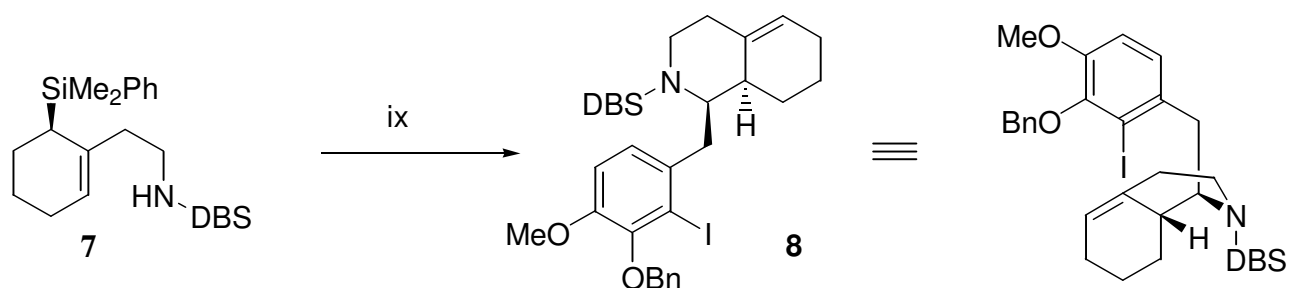
Reductive amination

cf Ginsberg's synthesis (step xix)

Clayden pp354-355



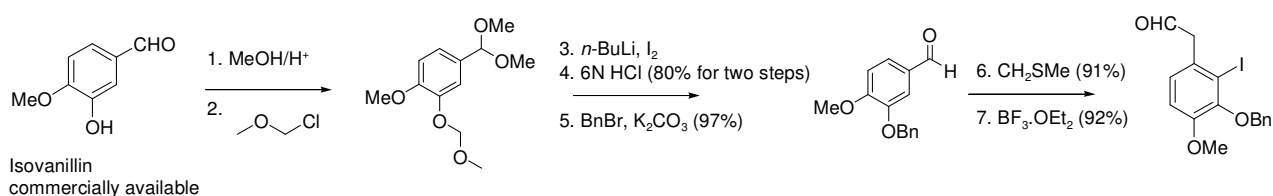
Sequence 3



• Step ix

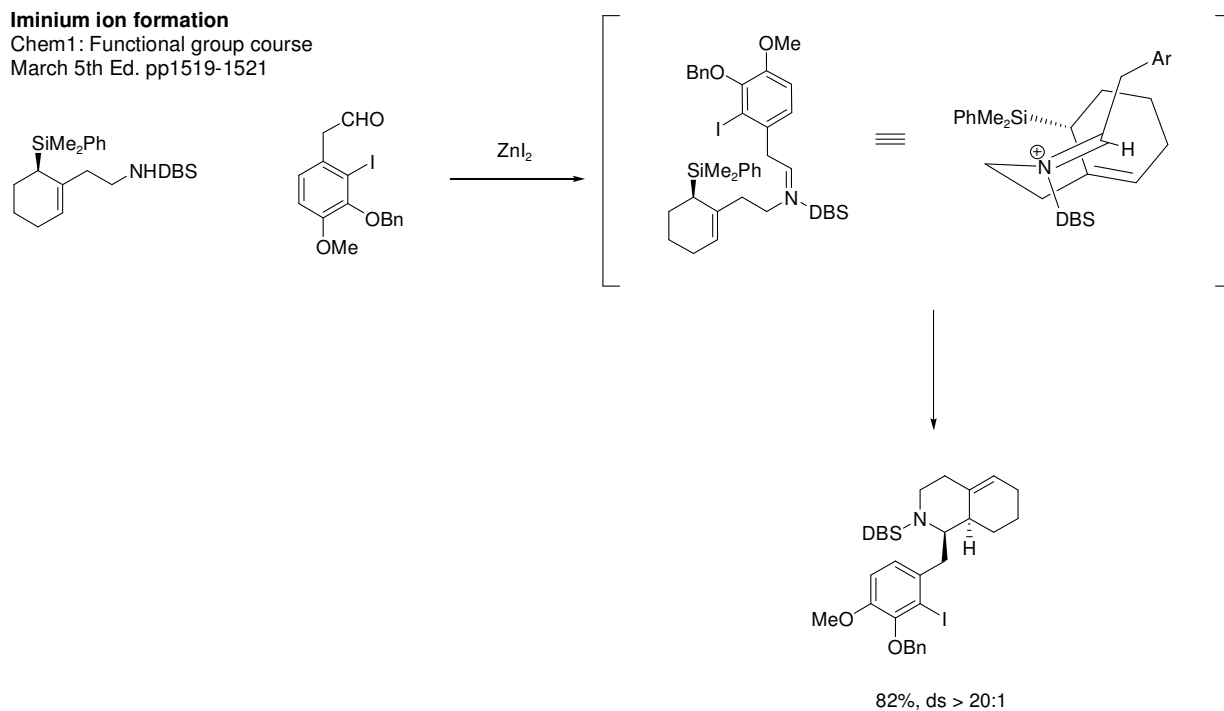
Preparation of aldehyde for step ix

Steps: 1. Acetal formation, 2. protection of alcohol as a MOM acetal, 3. Iodination using directed lithiation, 4. acetal and ketal hydrolysis, 5. benzylation, 6. epoxide formation using sulfur ylide, 7. Lewis-acid catalysed rearrangement.

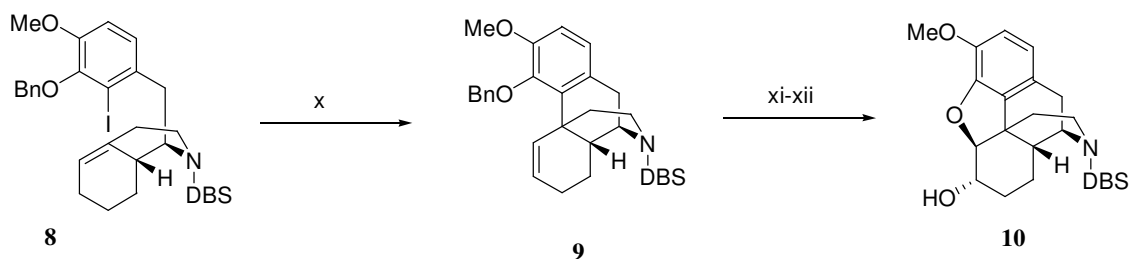


Iminium ion formation

Chem1: Functional group course
March 5th Ed. pp1519-1521



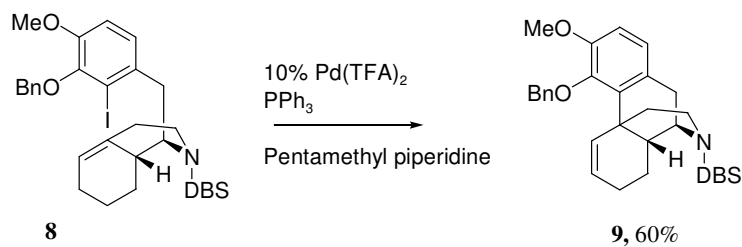
Sequence 4



Step x

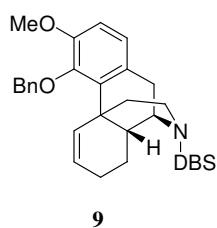
x. Intramolecular Heck reaction

Chem 4/5: Organometallics in synthesis
Clayden pp1321-1323



Steps xi-xii

xi. Debenzylation



xii. Epoxidation followed by *in situ* opening

Chem3: Conf analysis

