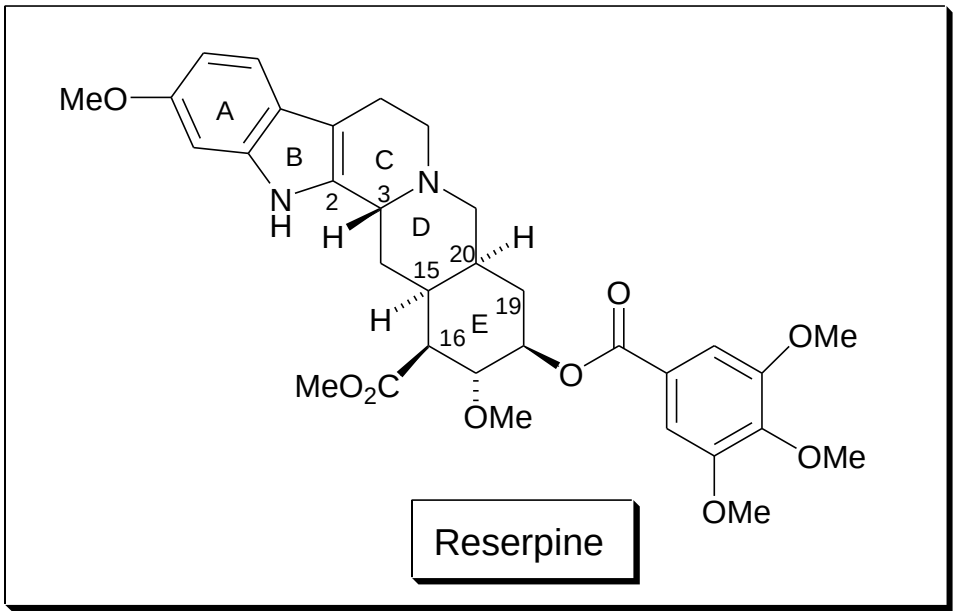
Lecture 36

12.1 Reserpine

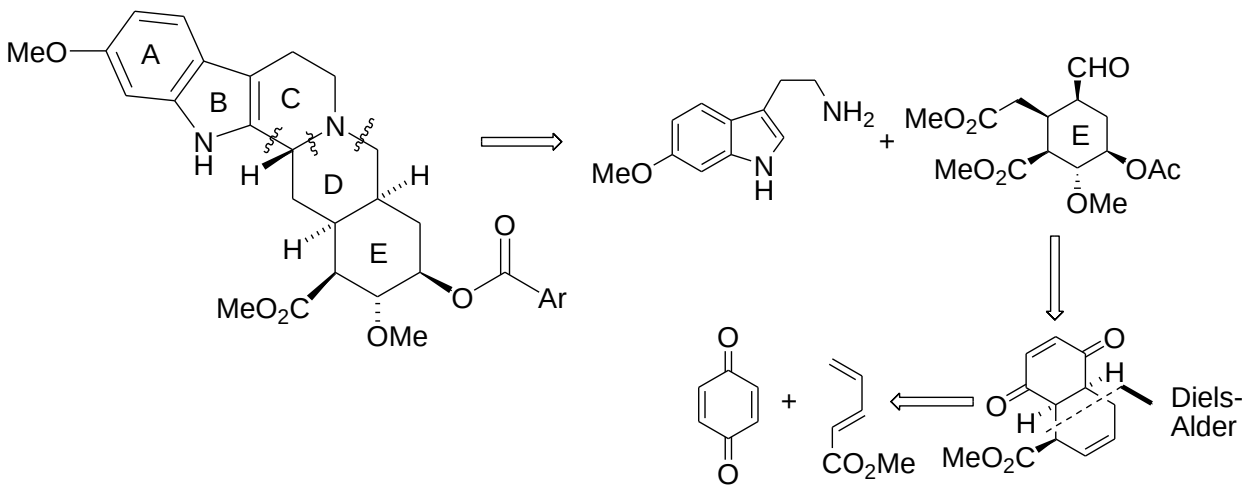


It is found, with other alkaloids, in the roots of the plant genus *Rauwolfia* and used in the treatment of some mental disorders as well as for the reduction of hypertension.

This lecture will focus on the Woodward total synthesis of reserpine (R. B. Woodward et al. *J. Am. Chem. Soc.* **1956**, *78*, 2023; *Tetrahedron* **1958**, *2*, 1).

12.1.1 Retrosynthetic Analysis

The strategy was based on building five contiguous stereocentres into a decalin derivative that could be opened to a monocyclic compound to form ring E (Scheme 1).

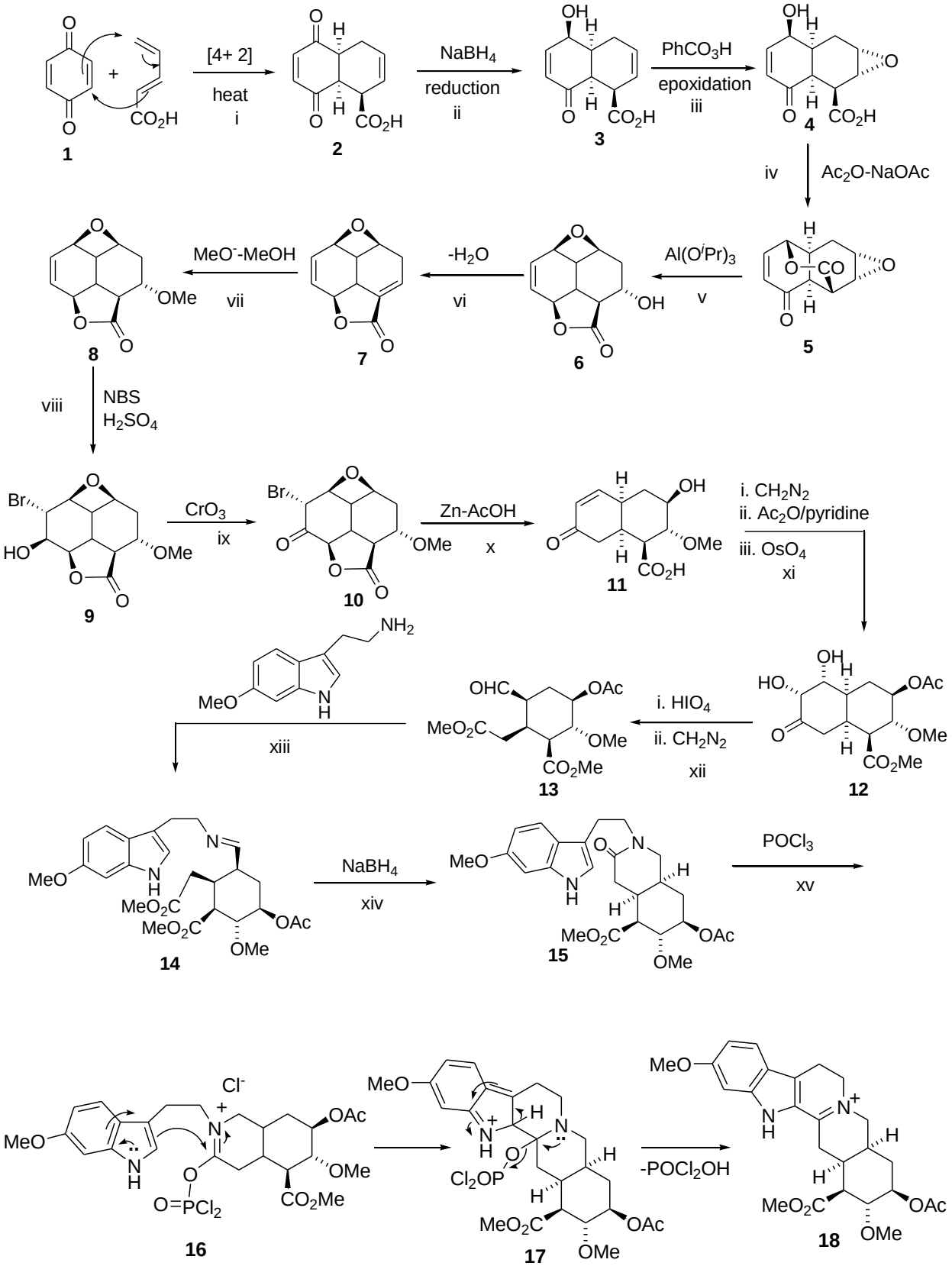


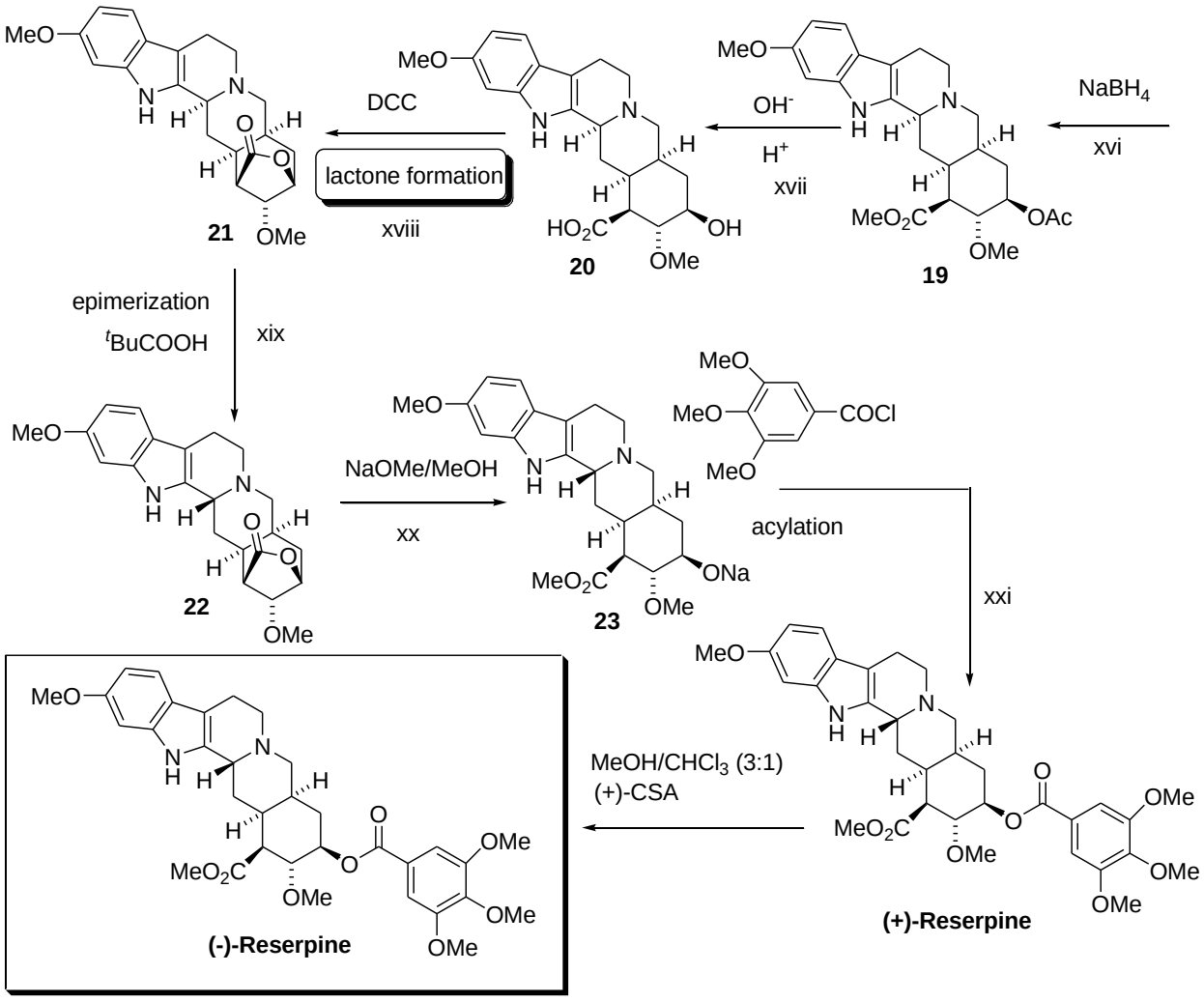
Scheme 1. Retrosynthetic Analysis

12.1.2 Total Synthesis

- The Diels-Alder reaction can lead to the ring junction having *cis* stereochemistry and the carboxyl group lie on the same side as the rings with respect to the ring junction (i) (Scheme 2). This step fixes the stereochemistry at C_{15}, C_{16} and C_{20} of reserpine.

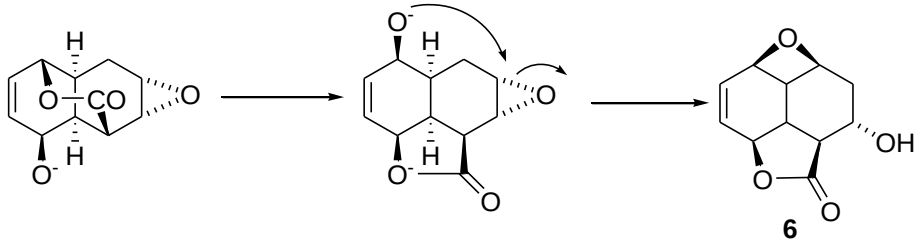
- $NaBH_4$ reduction of the less hindered of the two carbonyl groups of **2** can provide **3** (ii). The epoxidation of the isolated double bond with mCPBA at the less hindered side can afford **4** (iii) that could undergo dehydration to give the lactone **5** (iv).


[4+ 2]
heat
i
NaBH4
reduction
ii
PhCO3H
epoxidation
iii
iv
Ac2O-NaOAc
Al(OiPr)3
v
-H2O
vi
MeO--MeOH
vii
viii
NBS
H2SO4
CrO3
ix
Zn-AcOH
x
i. CH2N2
ii. Ac2O/pyridine
iii. OsO4
xi
i. HIO4
ii. CH2N2
xii
xiii
NaBH4
xiv
POCl3
xv
-POCl2OH
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18



Scheme 2. Total Synthesis

- Meerwein-Ponndorf-Verley reduction of **5** could convert the keto group into hydroxyl that can displace on the carbonyl of the six membered lactone ring, giving a five membered lactone, and the hydroxyl group so released can open the epoxide ring to afford **6** (Scheme 3).

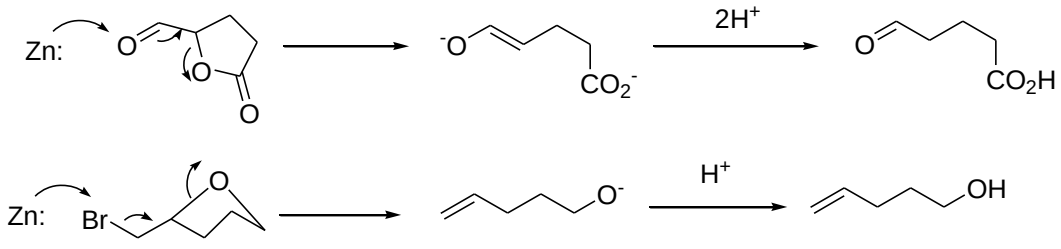


Scheme 3

- Dehydration of **6** can give α,β-unsaturated carbonyl compound **7** that could undergo conjugate addition at the less hindered α-side with methoxide to give **8** (vi and vii).

- NBS in acid could approach α-side of **8** to give a brominium ion that could be opened by water to give the biaxial bromo-alcohol **9** (viii) that could undergo mild oxidation to afford **10** (ix).

- Zn in AcOH can bring the reductive opening of both the lactone and the strained ether of **10** to give **11** (x) (Scheme 4).



Scheme 4

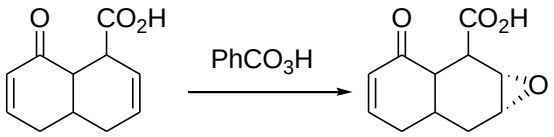
- Esterification of the carboxyl group using diazomethane, acetylation of the alcohol group using Ac_2O and dihydroxylation of the double bond can give **12** (xi) that could undergo oxidative cleavage followed by esterification of the new carboxyl group with diazomethane to give **13** (xii).

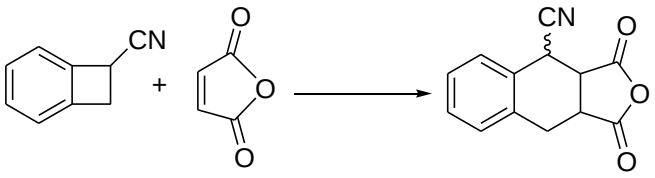
- Schiff base formation of **13** with 6-methoxytryptamine can give **14** that could be converted into **15** by $NaBH_4$ reduction of the imine double bond (xiii and xiv). Treatment of **15** with $POCl_3$ can bring ring closure as in the Bischler-Napieralski synthesis of isoquinoline, providing an imminium salt **18** via **16** and **17** (xv), which could be reduced using $NaBH_4$ to give **19** (xvi).

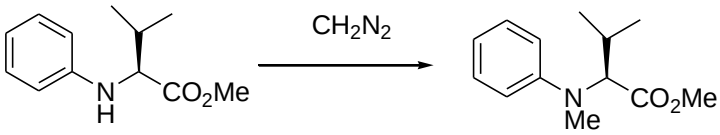
- Base hydrolysis of **19** can give **20** having free OH and COOH groups that could be joined to give a lactone **21** using DCC (xvii and xviii). Epimerization of the less stable **21** using t-butyric acid can give the required more stable **22** that could be converted into (±)-reserpine by opening of the lactone with MeOH followed by acylation using 3,4,5-trimethoxybenzoyl chloride. The (±)-reserpine could be resolved using CSA in a 3:1 mixture of MeOH and $CHCl_3$.

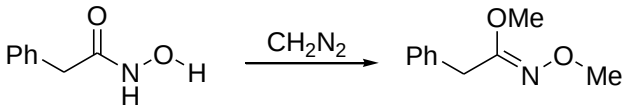
Problems

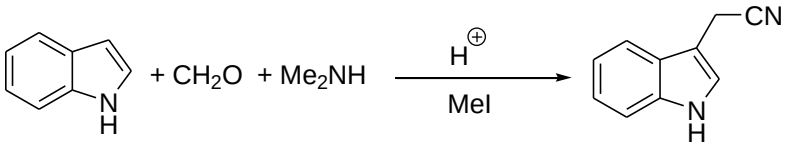
A. Complete the following reactions.

1. 

2. 

3. 

4. 

5. 

B. Explain the stereochemical principles of Diels-Alder reaction.

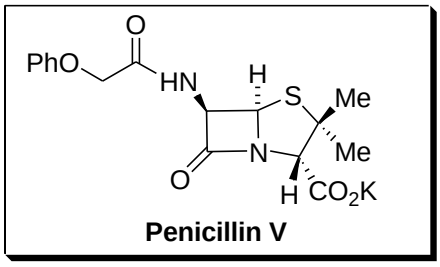
Text Books

R. O. C. Norman, J. M. Coxon, *Principles of Organic Synthesis*, CRC Press, London, 2009.

K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, VCH, Weinheim, 1996.

Lecture 37

12.2 Penicillin V

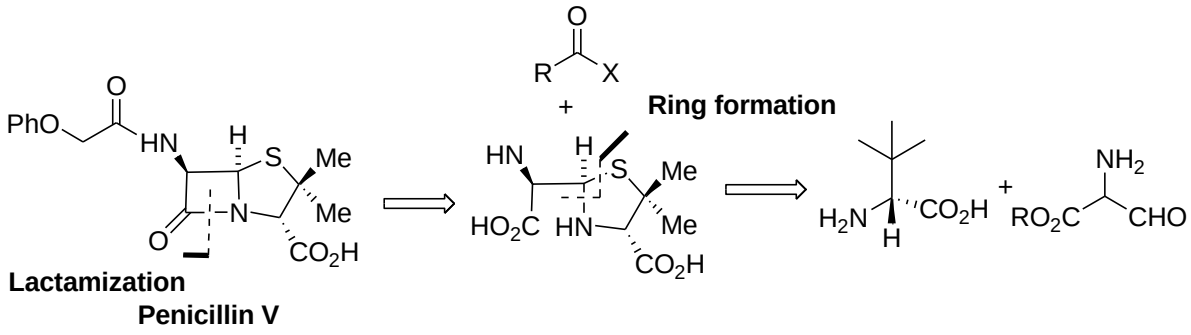


Penicillin V

Penicillins are produced from the mould *Penicillium notatum*, different strains produce different penicillins. They owe their importance to their powerful effect on various pathogenic organisms. This lecture will present Sheehan total synthesis of penicillin V (*J. Am. Chem. Soc.* **1959**, *81*, 3089).

12.2.1 Retrosynthetic Analysis

The synthetic strategy employed by Sheehan for penicillin synthesis is shown in Scheme 1.

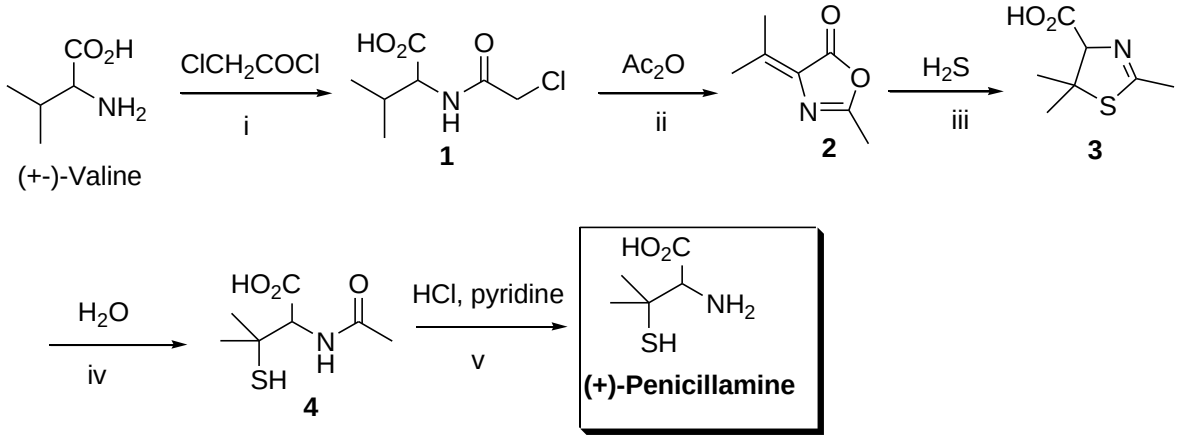


Scheme 1

12.2.2 Total Synthesis

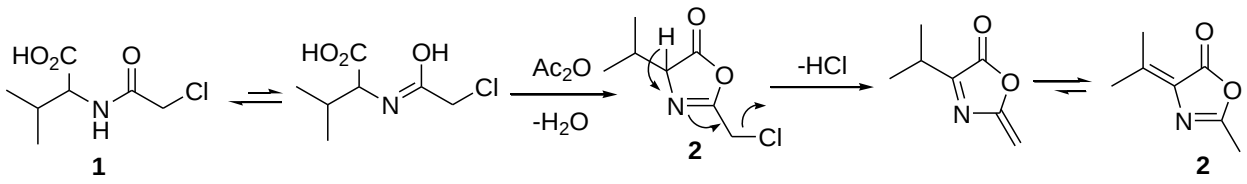
12.2.2.1. Synthesis of (+)-Penicillamine

Scheme 2 shows the synthesis of (+)-penicillamine from (±)-valine.



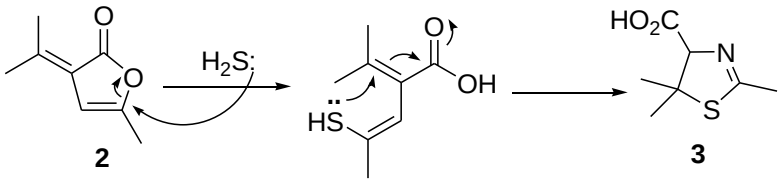
Scheme 2. Synthesis of Penicillamine

- N-Acylation of (±)-valine with α-chloroacetyl chloride gives **1** (i) that undergoes dehydrative cyclization with acetic anhydride to provide **2** (ii) by the elimination of HCl followed by a proton shift (Scheme 3).



Scheme 3

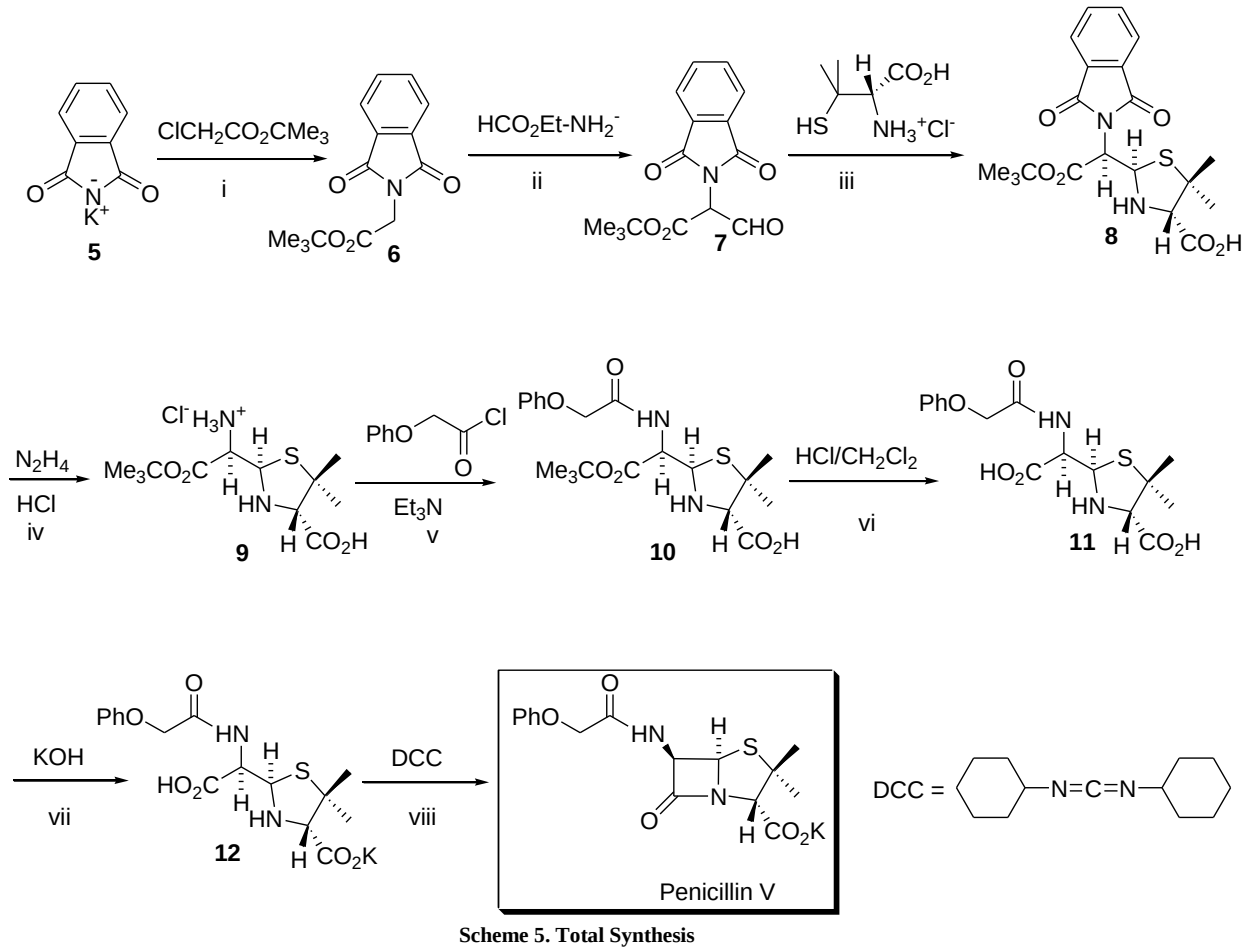
- The azlactone **2** can be cleaved by H_2S and the resulting thiol could cyclize via Michael-type addition to the α,β-unsaturated acid to give thiazoline **3** (iii) (Scheme 4) that could be opened in boiling water to afford **4** (iv). The N-acyl group of **4** could be removed by acid hydrolysis to yield (±)-penicillamine (v) that could be resolved using brucine to give the optically pure (+)-penicillamine.



Scheme 4

12.2.2.2 Synthesis of PenicillinV

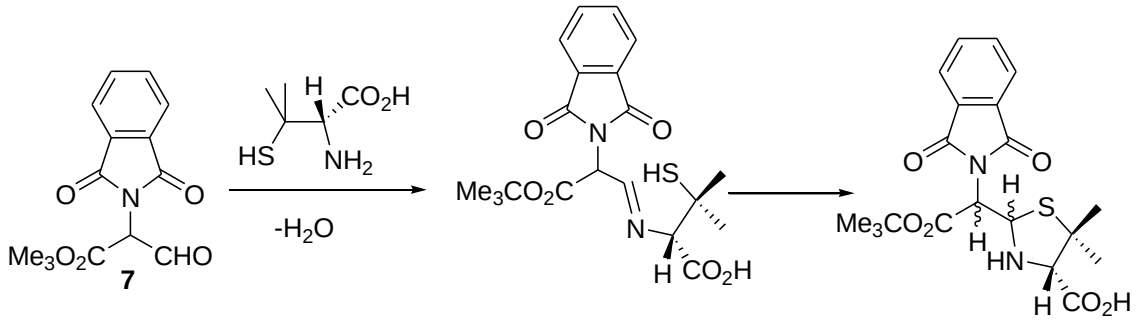
Scheme 5 describes the total synthesis of penicillin V.



Scheme 5. Total Synthesis

- Nucleophilic substitution of **5** with *t*-butyl chloroacetate gives **6** (Gabriel's synthesis, i) that undergoes cross Claisen condensation with ethyl formate to afford **7** (ii).

- The intermediate **7** with penicillamine hydrochloride at room temperature in sodium acetate buffer affords **8** as a mixture of four diastereomers via Schiff base formation followed by cyclization with the imine double bond (Scheme 6). However, the required **8** could be separated from the mixture of diastereomers.



Scheme 6

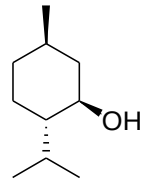
- The removal of the phthalimido group from **8** could be accomplished using hydrazine to afford **9** as a salt in the presence of HCl in acetic acid (iv).

- Acylation of the amino group of **9** in the presence of triethyl amine can give **10** (v) that could be converted into **11** by acid hydrolysis of t-butyl ester in dichloromethane at 0 ^{o}C (vi).

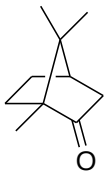
- The intermediate **11** in the presence of KOH can give the potassium salt (vii) that could be cyclized using DCC to give the potassium penicillinate (viii). Penicillin V can be extracted after acidification with phosphoric acid which crystallizes from aqueous solution at pH 6.8.

Problems

A. How will you synthesize the following compounds?

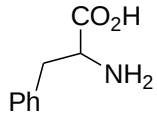


Menthol

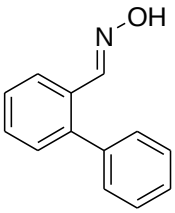


Camphor

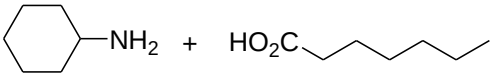
B. Predict the major products for the following reactions.

1. 

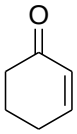
$ClCH_2COCl$, Ac_2O

2. 

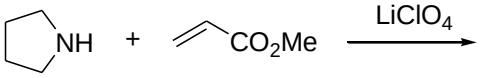
DCC, CH_2Cl_2

3. 

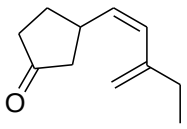
DCC, CH_2Cl_2

4. 

i. NaN_3, AcOH
ii. PPh_3

5. 

$LiClO_4$

6. 

NaH

Text Books

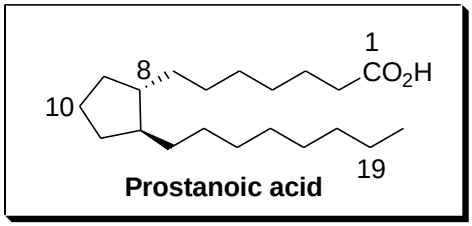
R. O. C. Norman, J. M. Coxon, *Principles of Organic Synthesis*, CRC Press, London, 2009.

K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, VCH, Weinheim, 1996.

Lecture 38

12.3 Prostaglandins E_2 and F_{2a}

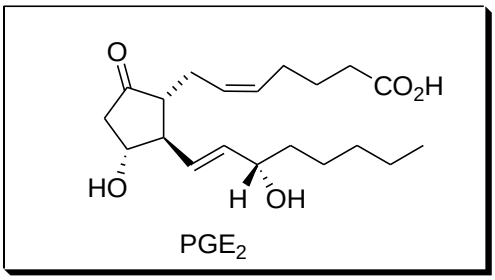
Prostaglandins are a series of closely related hormones that are derivatives of 'prostanoic acid':

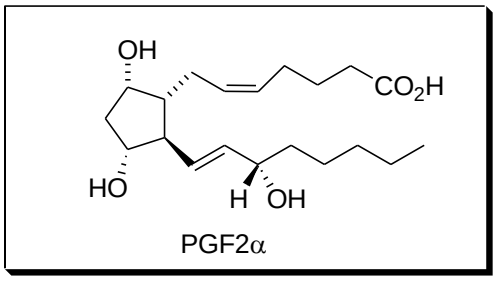


Parent skeleton of the prostaglandin family

Prostaglandins are present in many mammalian tissues at very low concentrations and exhibit potent effects on various types of smooth muscle. They are of considerable medical interest for the control of hypertension.

Prostaglandins E_2 (PGE_2) and F_{2a} ($PGF_{2\alpha}$) are two of the six primary prostaglandins. The E series have a β-hydroxy ketone structure in the ring and differ in the degree of unsaturation in the side-chain, while F series have a β-hydroxy group in the ring and likewise differ in the extent of unsaturation in the side-chains.

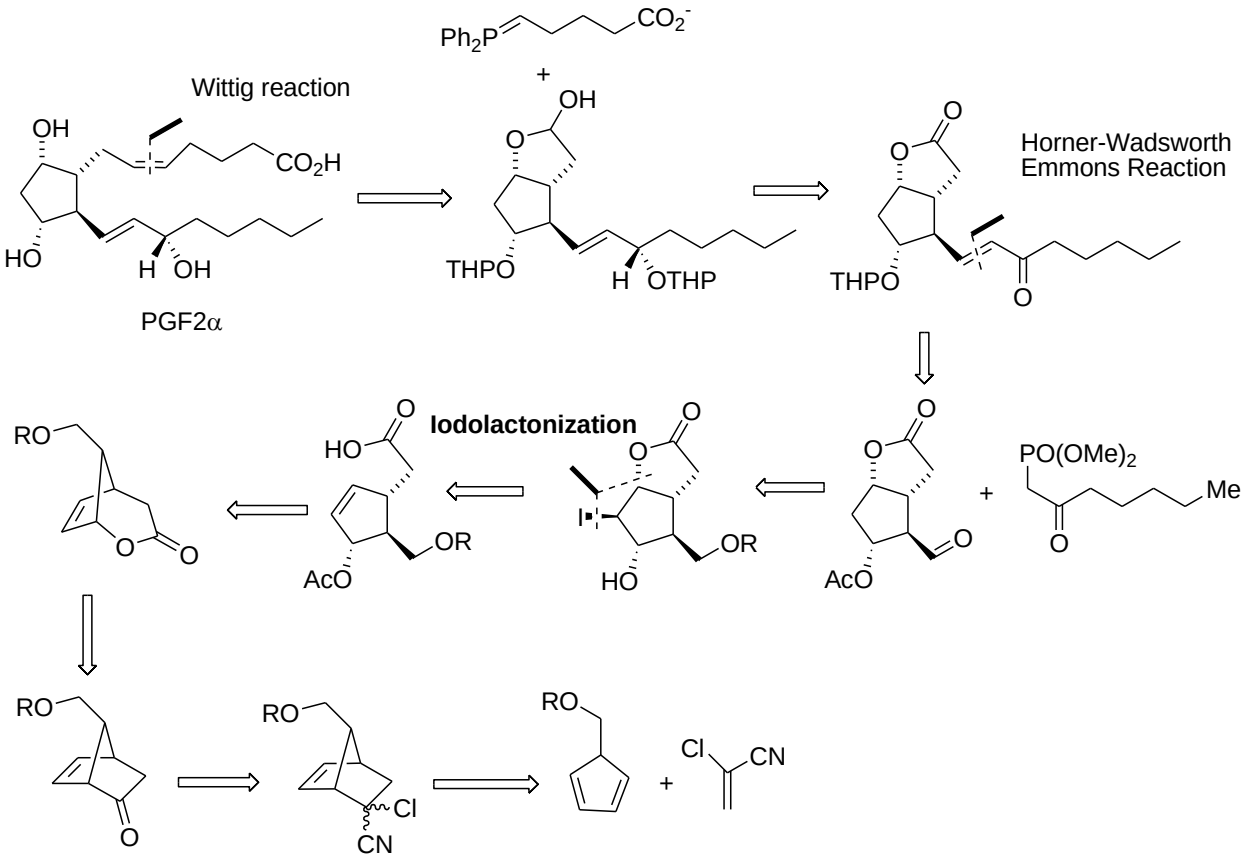




This lecture presents E. J. Corey's approach for the synthesis of PGE2 and PGF2a (*J. Am. Chem. Soc.* **1969**, *91*, 5675; *ibid* **1971**, *93*, 1489; *ibid* **1972**, *94*, 8616).

12.3.1 Retrosynthetic Analysis of PGF_{2a}

Scheme 1 outlines the general features of Corey's strategy for PGF_{2a} synthesis.

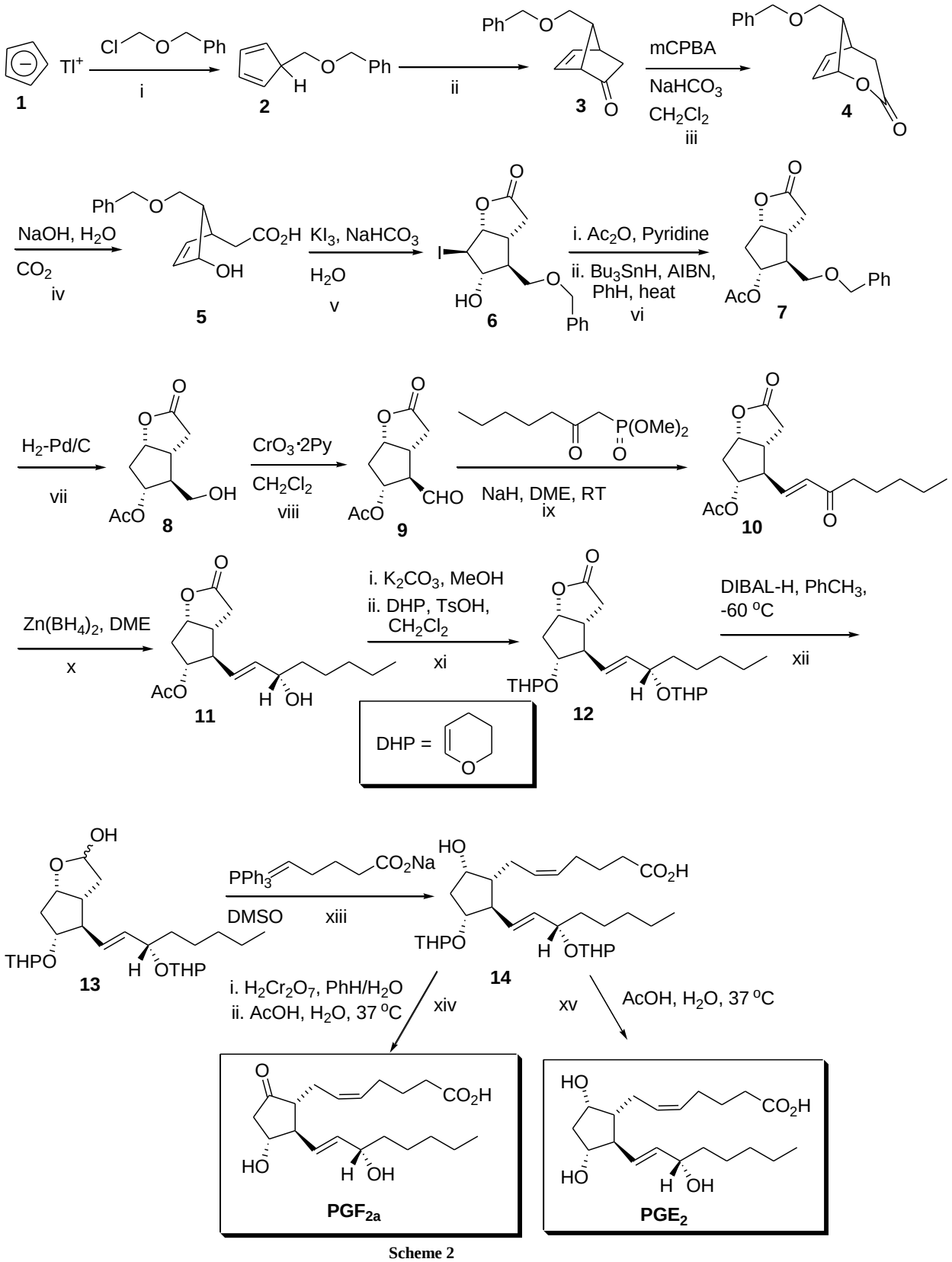


Scheme 1

12.3.2 Total Synthesis

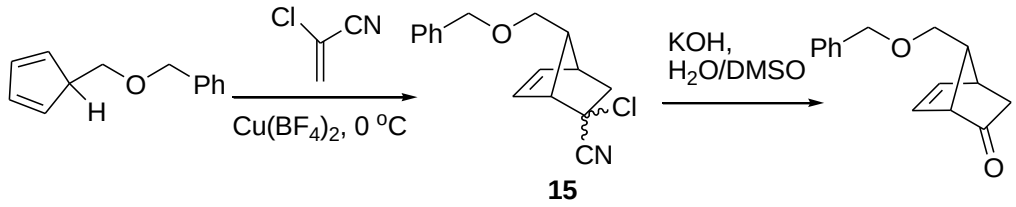
Scheme 2 presents the synthesis of PGE_2 and $PGF_{2a.}$

- Thallium(I) cyclopentadiene **1**, prepared from cyclopentadiene with $TlSO_4$ and KOH in water, could be alkylated using benzyl chloromethyl ether, which has the advantage that subsequent debenzylation can be more easily accomplished (i).


1
Tl+
Cl O Ph
i
2
H
O Ph
ii
3
Ph O
O
mCPBA
NaHCO3
CH2Cl2
iii
4
Ph O
O
O
NaOH, H2O
CO2
iv
5
Ph O
CO2H
OH
KI3, NaHCO3
H2O
v
6
O
O
I
HO
O
Ph
i. Ac2O, Pyridine
ii. Bu3SnH, AIBN,
PhH, heat
vi
7
O
O
AcO
O Ph
H2-Pd/C
vii
8
O
O
AcO
OH
CrO3·2Py
CH2Cl2
viii
9
O
O
AcO
CHO
P(OMe)2
O O
NaH, DME, RT
ix
10
O
O
AcO
O
Zn(BH4)2, DME
x
11
O
O
AcO
H OH
i. K2CO3, MeOH
ii. DHP, TsOH,
CH2Cl2
xi
12
O
O
THPO
H OTHP
DIBAL-H, PhCH3,
-60 °C
xii
DHP =
O
13
OH
O
THPO
H OTHP
PPh3
CO2Na
DMSO
xiii
14
HO
CO2H
THPO
H OTHP
i. H2Cr2O7, PhH/H2O
ii. AcOH, H2O, 37 °C
xiv
xv
AcOH, H2O, 37 °C
O
CO2H
HO
H OH
PGF2a
HO
CO2H
HO
H OH
PGE2

Scheme 2

- The copper(II)-catalyzed [4:2] cycloaddition of **2** with 2-chloroacrylonitrile can give **15** that could be hydrolyzed using KOH in DMSO to afford **3** (Scheme 3) (ii).



15

Scheme 3

- Baeyer-Villiger oxidation of the ketone **3** can give lactone **4** resulting from migration of secondary carbon in preference to the primary carbon (iii).
- The lactone **4** can be hydrolyzed with aqueous NaOH and the free acid **5** could be obtained by neutralization with CO_2 (iv). The latter could be iodolactonized with KI_3 to afford **6** having five asymmetric centres (v).
- Acetylation of the OH group employing acetic anhydride as an acylating agent followed by deiodination using tributyltin hydride (Bu_3SnH) in the presence of radical initiator AIBN can give **7** (vi) that could be debenzylated by hydrogenolysis to afford **8** (vii).

- The PDC promoted alcohol oxidation of **8** can give the aldehydes **9** (viii) that could undergo Wadsworth-Emmons reaction with the anion of dimethyl 2-oxoheptyl phosphonate to give **10** (ix).

- The $Zn(BH_4)_2$ mediated reduction of the carbonyl group of the side-chain can yield **11** (x). The protection of OH groups of **11** can be readily accomplished with DHP in the presence of TsOH to afford 12 (xi).

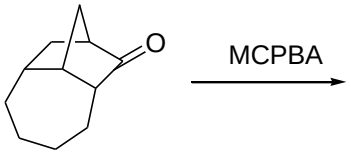
- The selective reduction of **11** to lactol **12** using DIBAL-H (xii) followed by Wittig reaction on the masked aldehydes in DMSO with the phosphorus ylide can afford **13** (xiii).

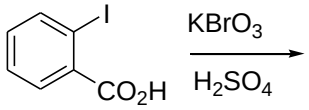
- The resultant prostanoid material **13** could be converted into prostaglandins E_2 by oxidation of the unprotected hydroxyl group followed by aqueous acidic hydrolysis (xv), whilest the aqueous acid hydrolysis of **13** could afford $F_{2\alpha}$ (xiv).

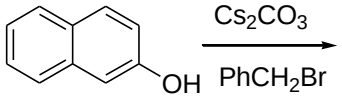
Problems

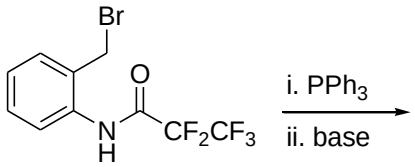
A. Outline synthetic route for oleic acid.

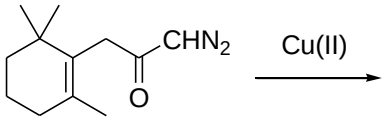
B. Complete the following.

1. 

2. 

3. 

4. 

5. 

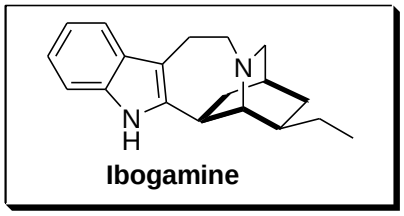
Text Books

R. O. C. Norman, J. M. Coxon, *Principles of Organic Synthesis*, CRC Press, London, 2009.

K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, VCH, Weinheim, 1996.

Lecture 39

12.4 Ibogamine

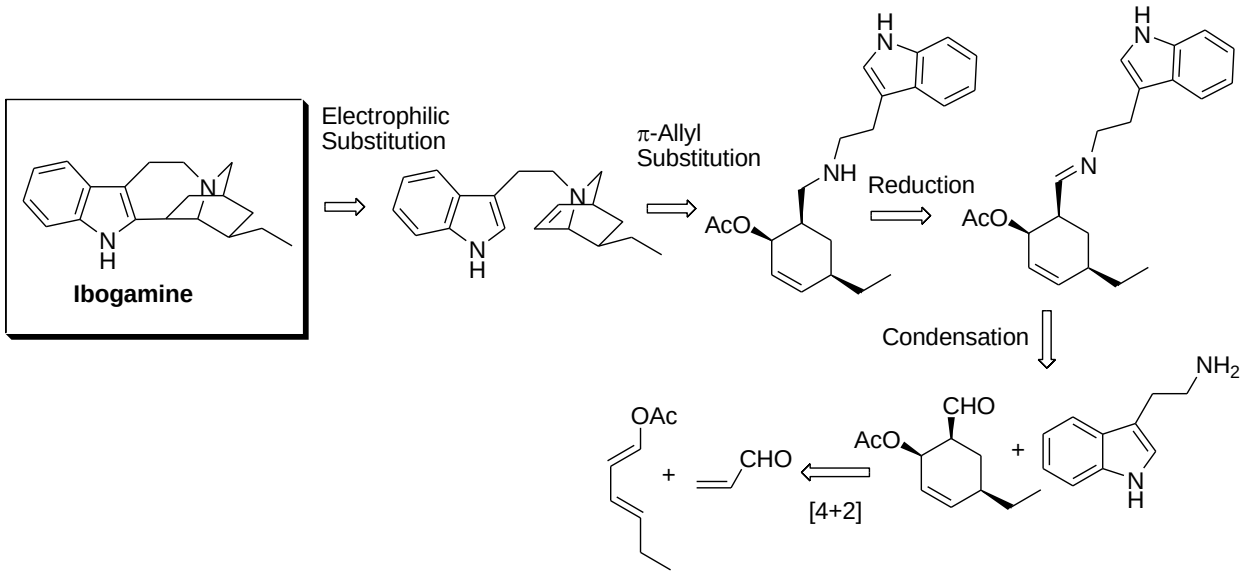


Ibogamine

Ibogamine is an alkaloid in the oboga family that has the clinically important antitumor alkaloid vinblastine. Hence, efficient synthetic approaches for the construction of the family of compounds have been stimulated. This section focuses on a short, stereocontrolled synthesis of ibogamine (B. M. Trost et al., *J. Am. Chem. Soc.* **1978**, *100*, 3930).

12.4.1 Retrosynthetic Analysis

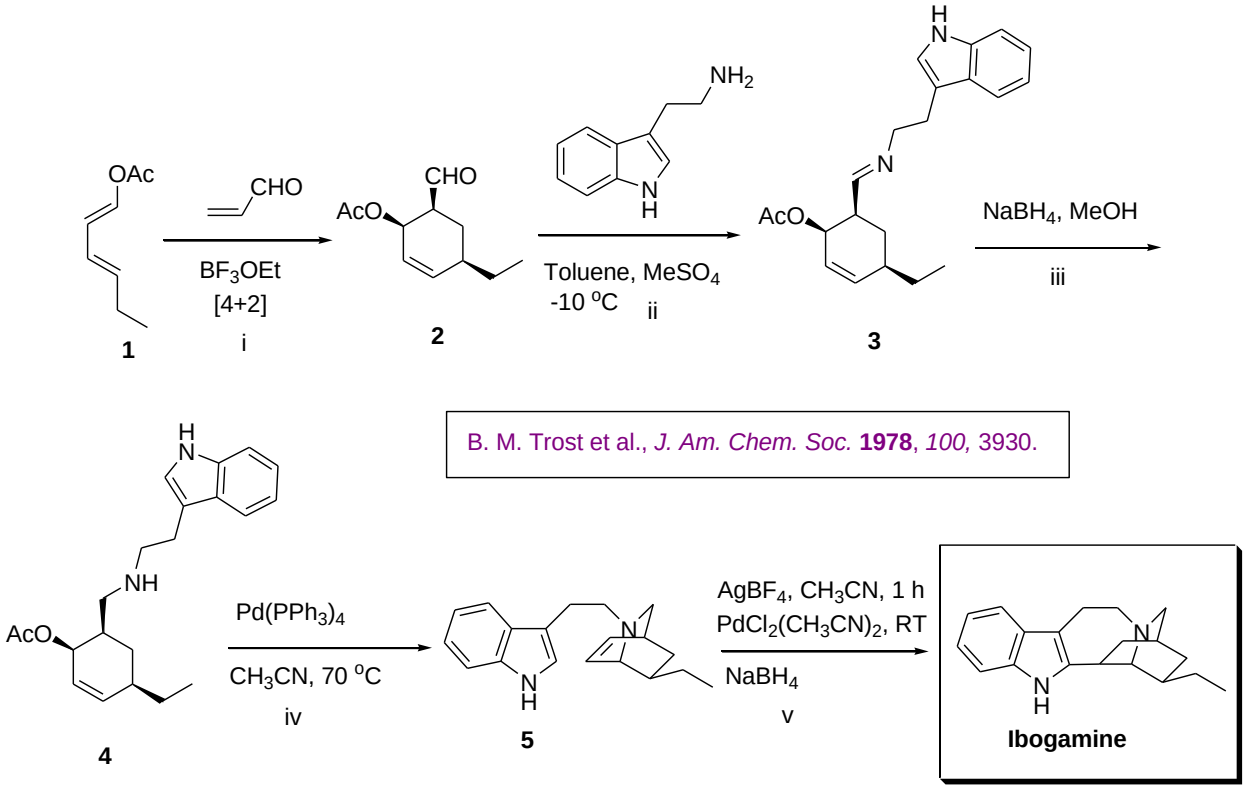
Scheme 1 outlines the common featurs of Trost's strategy for ibogamine synthesis:



Scheme 1

12.4.2 Synthesis of Ibogamine

The synthesis of ibogamine could be accomplished in five steps employing Diels-Alder reaction as key step to control the stereochemistry (Scheme 2).



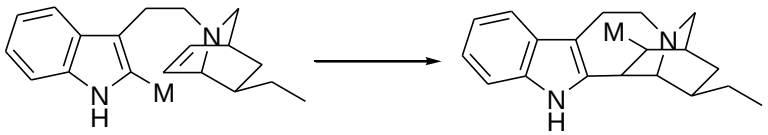
Scheme 2

- The Diels-Alder reaction of diene **1** with acrolein could afford the six-membered ring **2** having all the three substituents *cis* (i). Although, it is immaterial for the acetoxy group, the *cis* relationship between the ethyl and aldehydes groups is required to obtain the right stereochemistry of the target molecule.

- The Schiff base formation of **2** with tryptamine can give **3** (ii) that could be readily reduced using $NaBH_4$ to afford **4** (iii).

- The intermediate **4** may undergo reaction with Pd(0) to give □-allylic complex with a loss of acetate ion, that could react with the nucleophilic nitrogen atom of the amino group to afford **5** (iv).

- The $PdCl_2$ effected electrophilic substitution of the indole ring can give metal salt complex (Scheme 3) that could be reduced using $NaBH_4$ to afford the target molecule (v). The presence of silver ion increases the reactivity of the process.

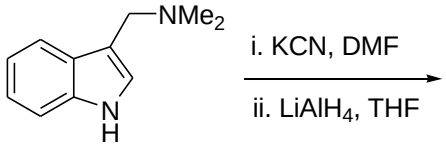


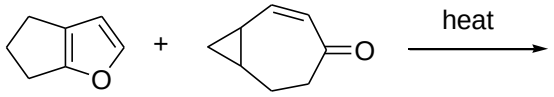
M = silver-palladium salt complex or partially ionized palladium salt

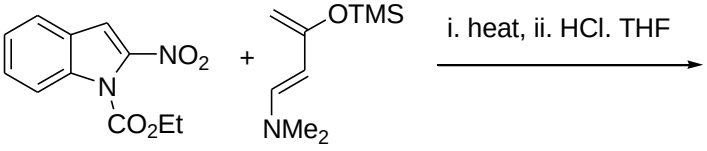
Scheme 3

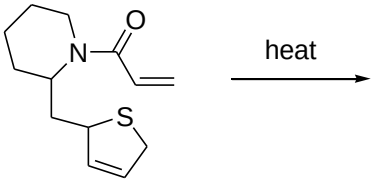
Problems

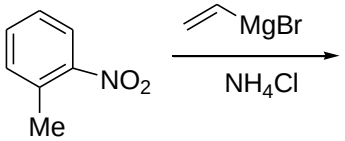
Complete the following with major products.

1. 

2. 

3. 

4. 

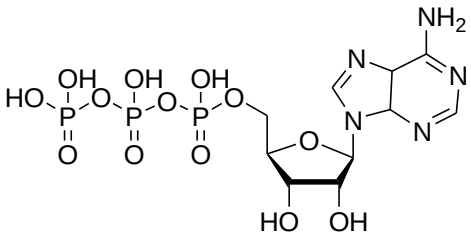
5. 

Text Book

R. O. C. Norman and J. M. Coxon, *Principles of Organic Synthesis*, CRC Press, London, 2009.

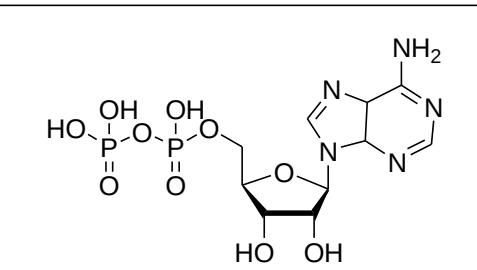
Lecture 40

12.5 Synthesis of Adenosine Triphosphate (ATP)



Adenosine Triphosphate (ATP)

ATP, in conjunction with its diphosphate, ADP, acts as a reversible phosphorylating couple and energy store. For example, it is concerned with the supply of energy for muscular contraction.



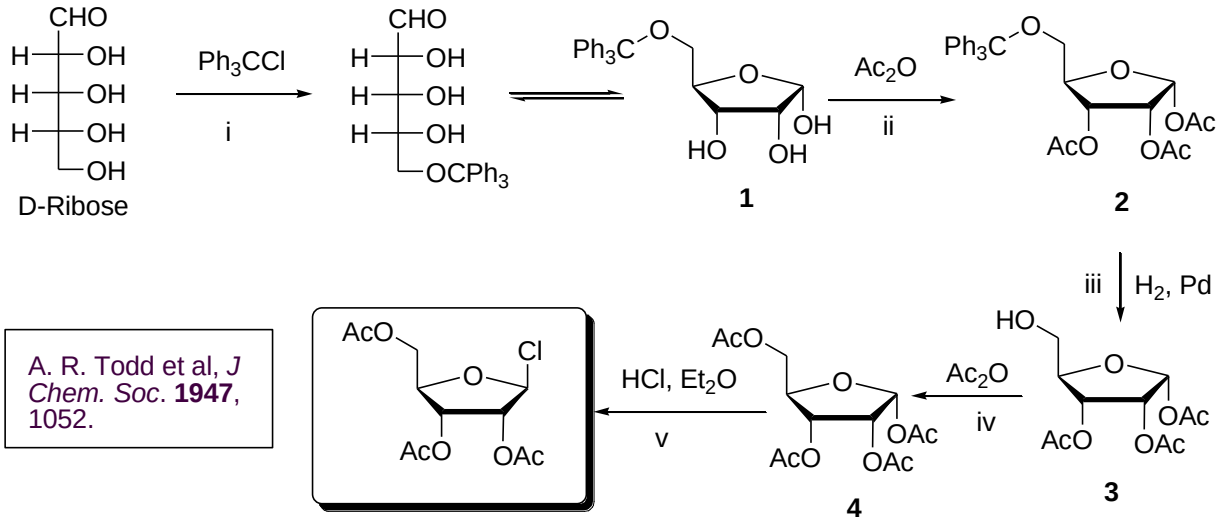
Adenosine Diphosphate (ADP)

Synthesis of β-Chloro-2,3,5-Triacetyl-D-Ribofuranose

The synthesis of β-chloro-2,3,5-triacetyl-D-ribofurance from D-ribose could be accomplished in five steps (Scheme 1).

- The selective reaction of the primary OH group of D-ribose with triphenylmethyl chloride ensures the sugar to adopt the furanose ring **1** system (i) that could be transformed into **3** via **2** by acetylation (ii) followed by removel of the triphenylmethyl group of using hydrogenation (iii).

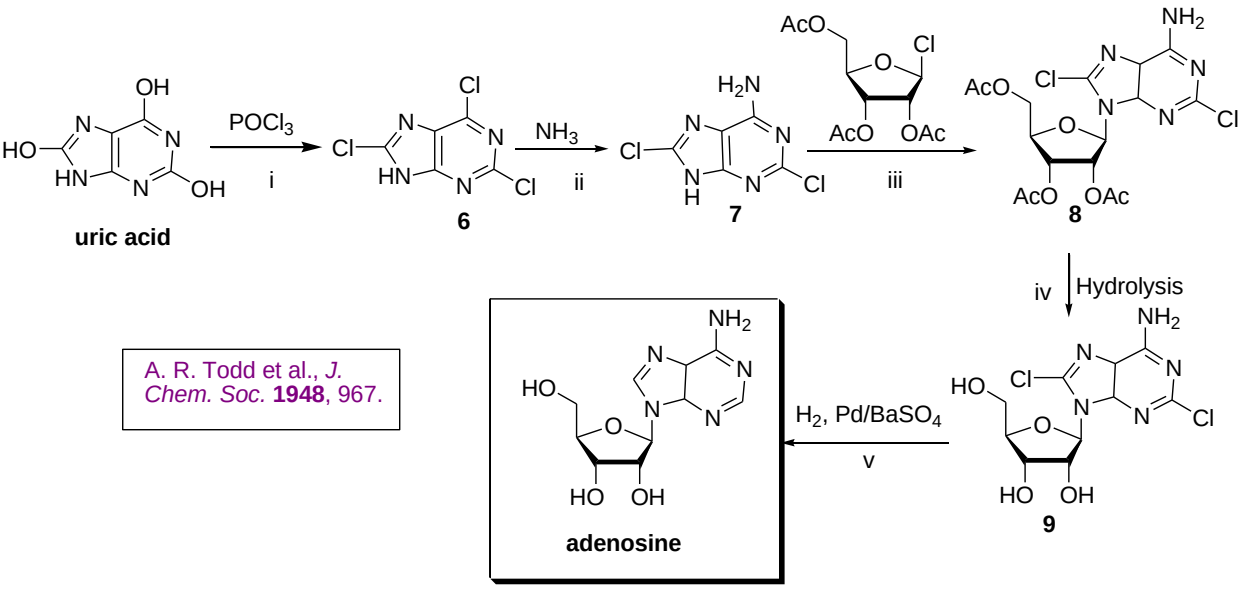
- Acetylation (iv) followed by S_N2 reaction at the carbon next to the ring oxygen of **4** using HCl (v) give the target molecule.



Scheme 1

Synthesis of Adenosine

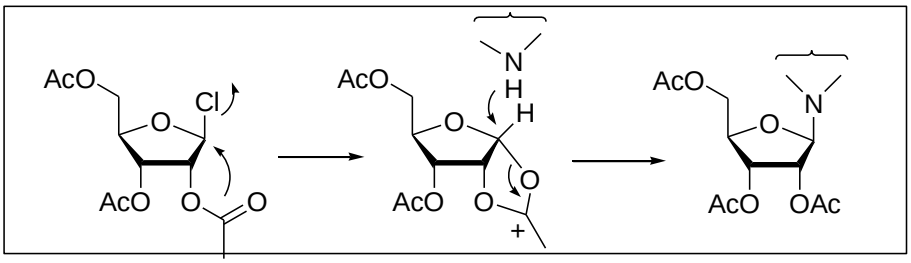
Uric acid could also be converted into adenosine in five steps (Scheme 2).



Scheme 2

- Uric acid could be converted into **6** by reaction with $POCl_3$ (i) that could undergo nuleophilic substitution selectively at 6-position with NH_3 to afford **7** (ii).

- Reaction of **7** with the chloro-furanoside gives **8**, presumably as a result of the formation of an acetoxonium ion followed by an S_N2 reaction (iii) (Scheme 3).



Scheme 3

- Hydrolysis of the acetyl groups of **8** (iv) followed by hydrogenolysis of the C-Cl bonds of **9** (v) gives the target adenosine.

Synthesis of ATP

The synthesis of ATP can be accomplished in eight steps form the above synthesized adenosine (Scheme 4).

- The 2- and 3-hydroxyl groups of the furanose ring of adenosine could be protected by the formation of ketal to afford ketal **10** (i).

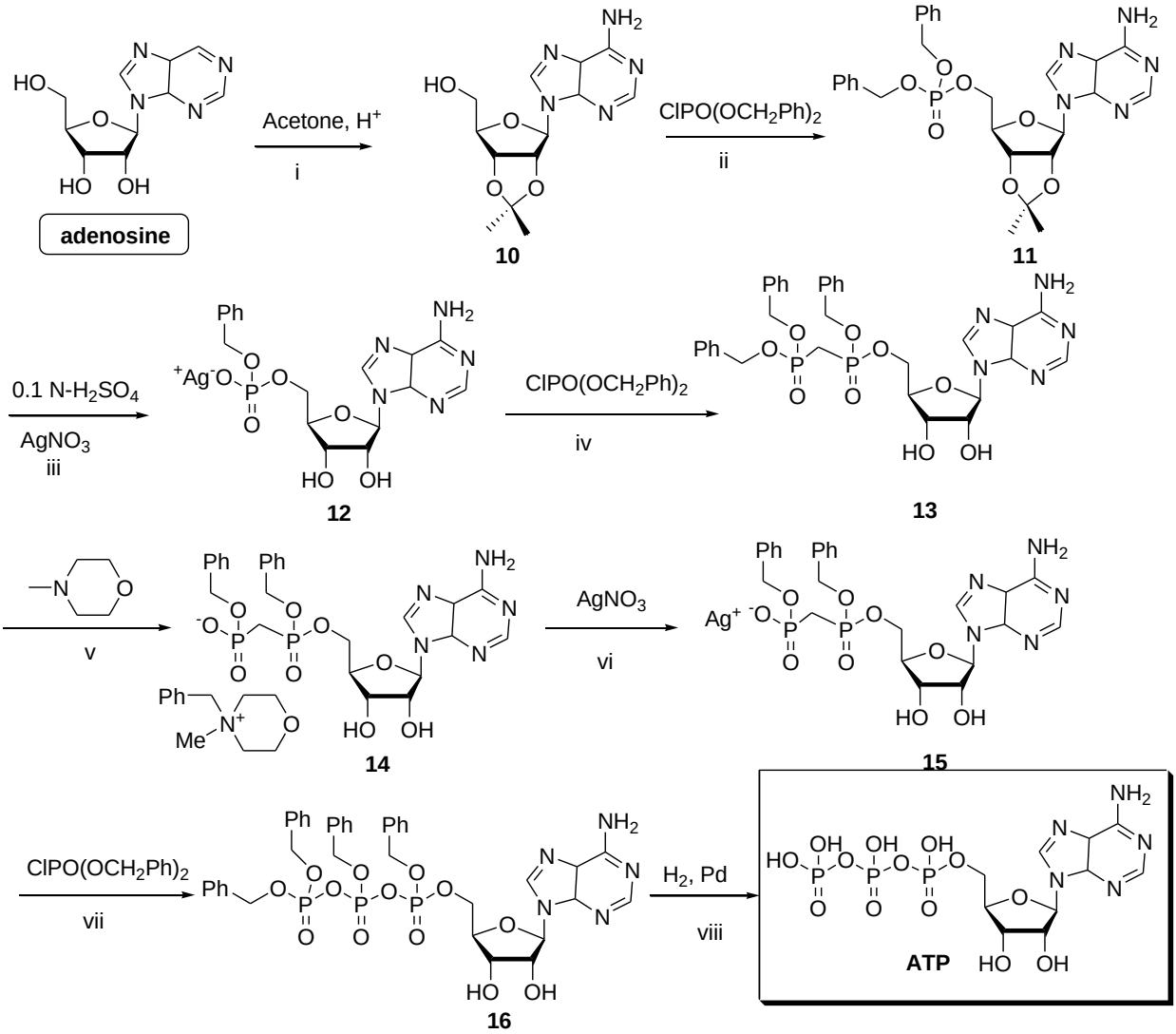
- Phosphorylation of **10** could be effected to give **11** at a low temperature and the removal of HCl can be performed using pyridine as a solvent (ii).

- Mild acid hydrolysis of **11** leads to the formation of **12** by removal of the one of benzyl groups along with the isopropylidene group (iii). After removal of the acid as barium sulfate, the product could be dissolved in alkali and precipitated as its silver salt.

- Phosphorylation of **12** in anhydrous CH_3COOH can give **13** (iv) that could be selectively debenzylated with *N*-methylmorpholine to afford **14** (v).

- Treatment of **14** with $AgNO_3$ can give **15** (vi) that could be phosphorylated in a mixture of CH_3CN and PhOH to afford **16** (vii).

- The four benzyl groups of **16** could be removed by hydrogenolysis and the target product, ATP, can be precipitated as its barium salt, liberated with sulfuric acid, and isolated as its acridinium salt (viii).



A. D. Todd et al., *J. Chem. Soc.* **1947**, 648; **1949**, 582.

Scheme 4

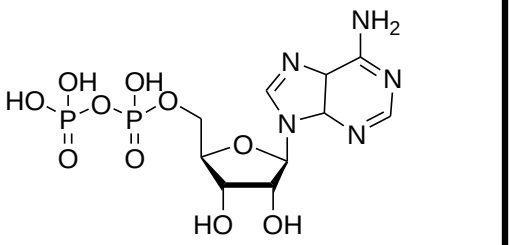
Preparation of Dibenzyl Chlorophosphonate

The chlorination of dibenzyl phosphate can give the phosphorylating agent, dibenzyl chlorophosphonate, in carbon tetrachloride (Scheme 5).

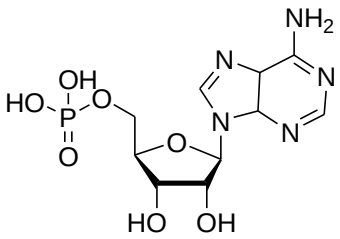
Scheme 5

Problems

A. Provide synthetic routes for ADP and AMP.

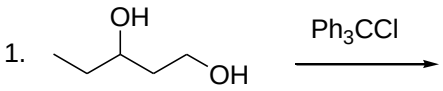


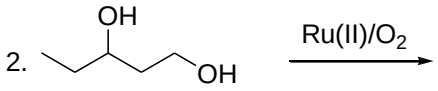
Adenosine Diphosphate (ADP)

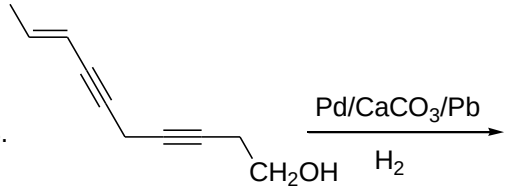


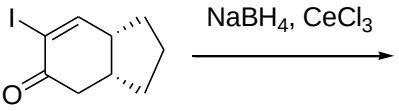
Adenosine Monophosphate (AMP)

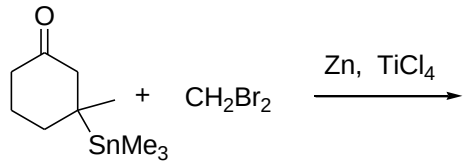
B. Complete the following reactions.

1. 

2. 

3. 

4. 

5. 

Text Books

R. O. C. Norman, J. M. Coxon, *Principles of Organic Synthesis*, CRC Press, London, 2009.

J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, New York, 2001.