



**Two Hundred Exercises in  
Mechanistic Organic Chemistry**



# **Two Hundred Exercises in Mechanistic Organic Chemistry**

**Gabriel Tojo Suárez**  
Titular Professor of Organic Chemistry  
University of Santiago de Compostela  
[qogatojo@uscmail.usc.es](mailto:qogatojo@uscmail.usc.es)



# Preface

Learning the mechanistic basis of Organic Chemistry is like mastering chess. In this game, one needs to know how to move the pieces before embarking in a match. Similarly, a student in Organic Chemistry begins by learning a list of simple reactions. This allows at a later stage to explain the complex mechanisms that intervene in many organic reactions and consist in a chain of simple reactions operating in a sequential way.

This book is aimed at students who have completed a learning cycle of Organic Chemistry and need to settle their mechanistic knowledge. One of these students should be able to solve each problem in about half an hour. A bachelor of Organic Chemistry should be able to do it in about ten minutes, while a professional Organic Chemist should consume less than two minutes.

There is no way to scientifically prove that a certain mechanism is correct. A mechanism can only be proved wrong. Mechanisms admitted as correct are those that explain the experimental data and have been able to resist all attempts at proving their falsehood. On the other hand, only a few simple reactions have been studied in detail from the mechanistic point of view.

The reactions depicted in this book are complex, and none have been studied in detail. Consequently, the proposed solutions represent the opinion of author. Proposing a reasonable mechanism is more relevant than hitting the right one. Many exercises admit more than one sensible mechanism and the proposed solutions represent reasonable, but not unique, answers.

No enterprise would meet an end if the goal is the perfection. It is better to make soon a good job than never a perfect one. Many people wait for the perfect moment to have children in order to give them the best possible education. Often the resulting delay causes them to be biologically unable to be parents. Bearing in mind that having children is so satisfactory that it is worth even in a very imperfect way, I have written this book. I hope to be able to be proud of this intellectual offspring in spite of its deficiencies.

Santiago, May 20th 2002

Gabriel Tojo



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# Abbreviations

15-crown-5	1,4,7,10,13-pentaoxacyclopentadecane	NBS	<i>N</i> -bromosuccinimide
Ac	acetyl, CH <sub>3</sub> C(=O)–	Pd/C	palladium on activated carbon
B:	base	Ph	phenyl
Bn	benzyl, PhCH <sub>2</sub> –	Piv	pivaloyl, Me <sub>3</sub> CC(=O)–
Boc	<i>tert</i> -butoxycarbonyl, <i>t</i> -BuOC(=O)–	PMB	<i>p</i> -methoxybenzyl, <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> –
Bu	<i>n</i> -butyl	PMP	<i>p</i> -methoxyphenyl, <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> –
<i>t</i> -Bu	<i>tert</i> -butyl, Me <sub>3</sub> C–	iPr	isopropyl, Me <sub>2</sub> CH–
cat.	catalytic	PPTS	pyridinium <i>p</i> -toluenesulfonate
Cbz	benzyloxycarbonyl, BnOC(=O)–	ref.	reflux
conc.	concentrated	rt	room temperature
CSA	camphorsulfonic acid	SEM	2-(trimethylsilyl)ethoxymethyl, TMSCH <sub>2</sub> CH <sub>2</sub> OCH <sub>2</sub> –
DABCO	4-diazabicyclo[2.2.2]octane	TBAF	tetrabutylammonium fluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	TBDPS	<i>tert</i> -butyldiphenylsilyl, <i>t</i> -BuPh <sub>2</sub> Si–
DMAP	<i>p</i> -(dimethylamino)pyridine	TBS	<i>tert</i> -butyldimethylsilyl, <i>t</i> -BuMe <sub>2</sub> Si–
DMSO	dimethyl sulfoxide, MeS(=O)Me	TES	triethylsilyl, Et <sub>3</sub> Si–
Et	ethyl, CH <sub>3</sub> CH <sub>2</sub> –	Tf	trifluoromethanesulfonyl (triflyl)
HMPA	hexamethylphosphoramide, (Me <sub>2</sub> N) <sub>3</sub> P=O	TFA	trifluoroacetic acid
KHMDS	KN(SiMe <sub>3</sub> ) <sub>2</sub>	THF	tetrahydrofuran
LDA	lithium diisopropylamide, iPr <sub>2</sub> NLi	THP	tetrahydropyran-2-yl
LHMDS	LiN(SiMe <sub>3</sub> ) <sub>2</sub>	TIPS	triisopropylsilyl
MCPBA	<i>m</i> -chloroperoxybenzoic acid	TMS	trimethylsilyl, Me <sub>3</sub> Si–
Me	methyl, CH <sub>3</sub> –	Tol	<i>p</i> -tolyl, <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> –
MOM	methoxymethyl, MeOCH <sub>2</sub> –	Tr	triphenylmethyl (trityl), Ph <sub>3</sub> C–
Ms	mesyl, MeSO <sub>2</sub> –	Troc	2,2,2-trichloroethoxycarbonyl
		Ts	<i>p</i> -toluenesulfonyl, <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> –



# EXERCISES

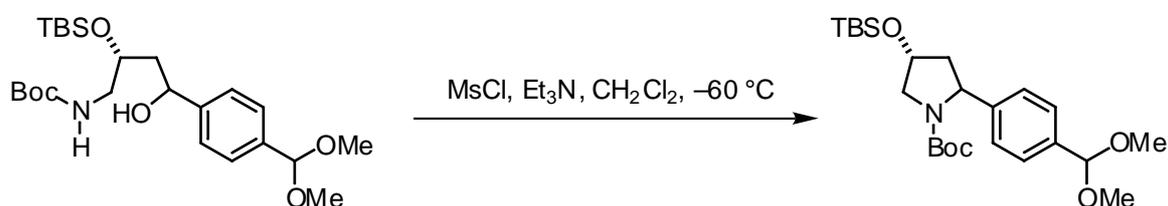


# Chapter 1

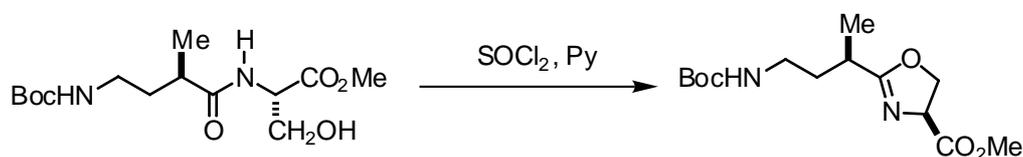
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## Good-Leaving Groups on $sp^3$ Carbons: Substitution and Elimination Reactions of Simple Alkenes

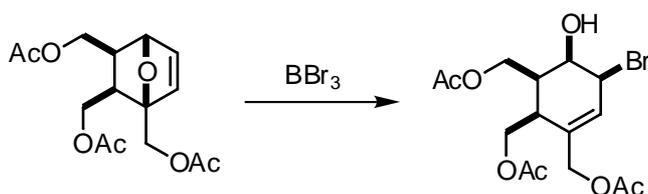
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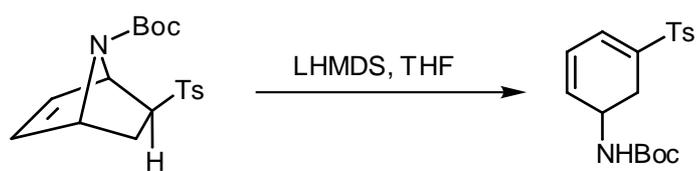
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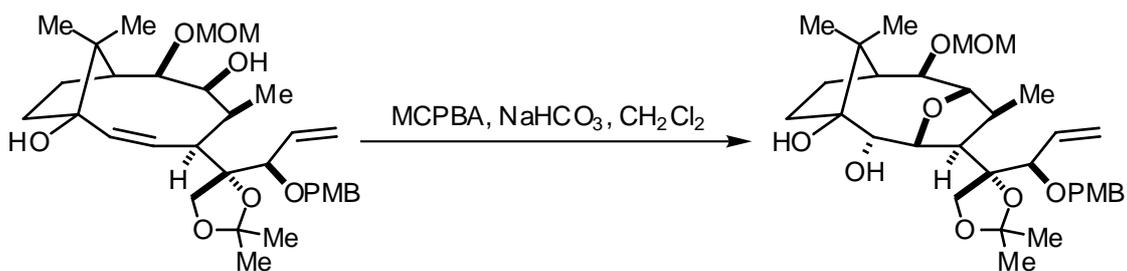
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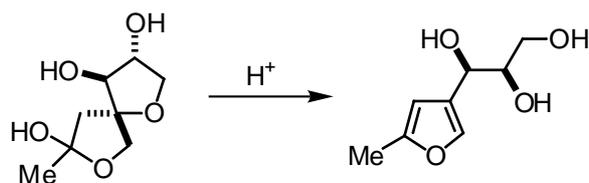
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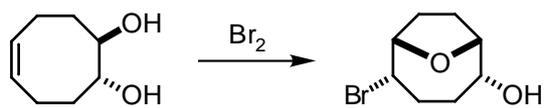
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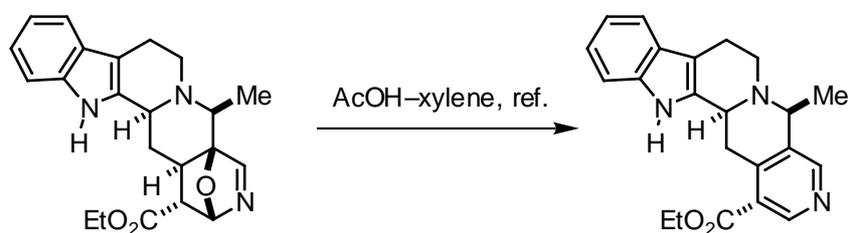
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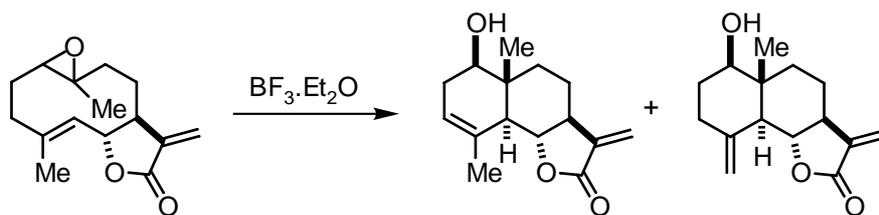
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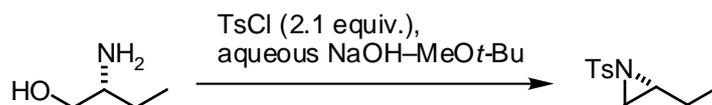
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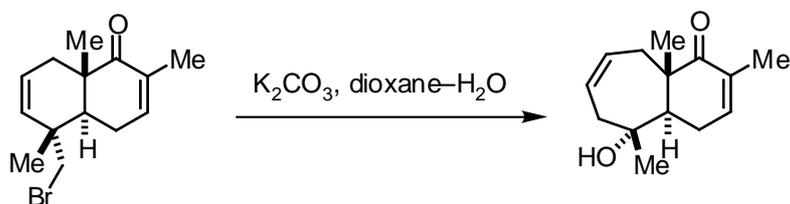
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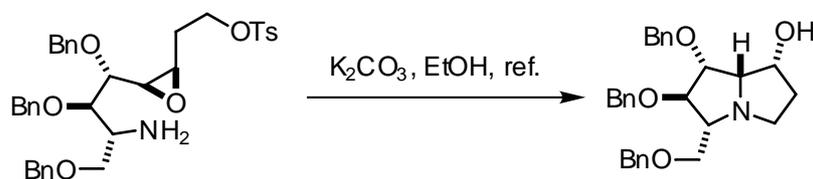
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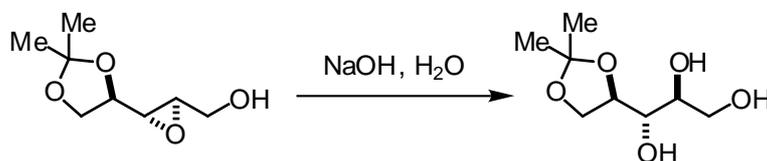
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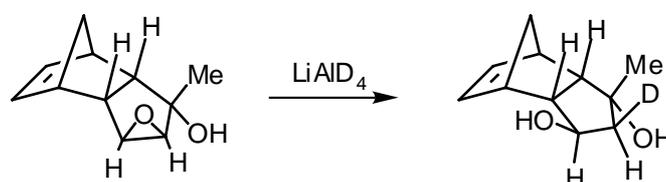
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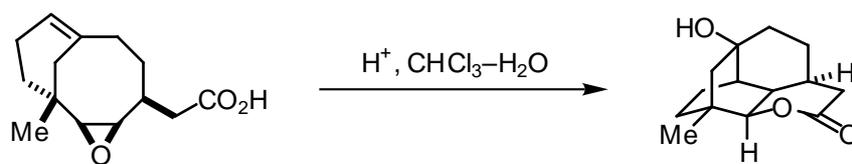
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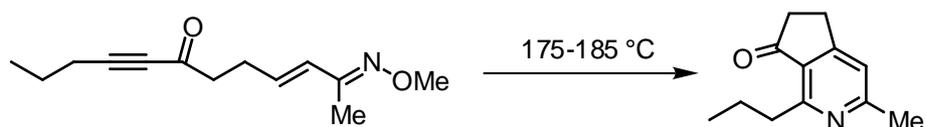
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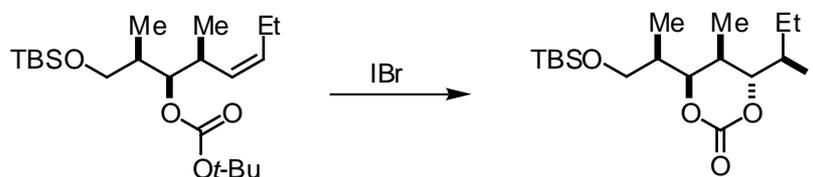
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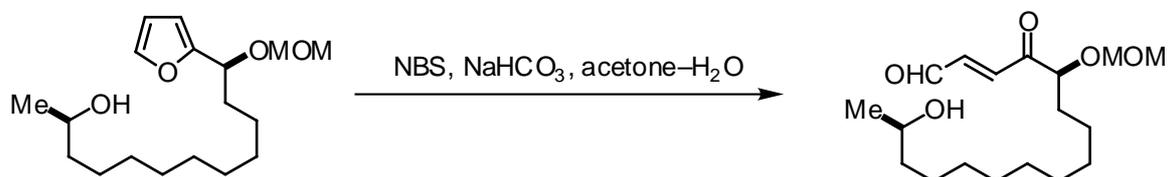
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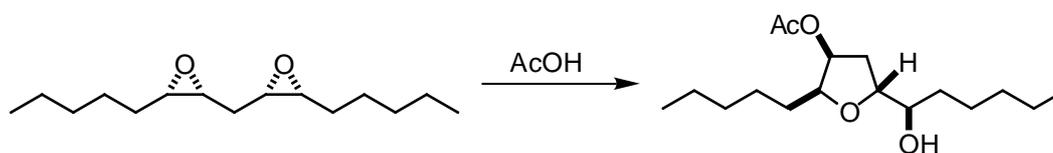
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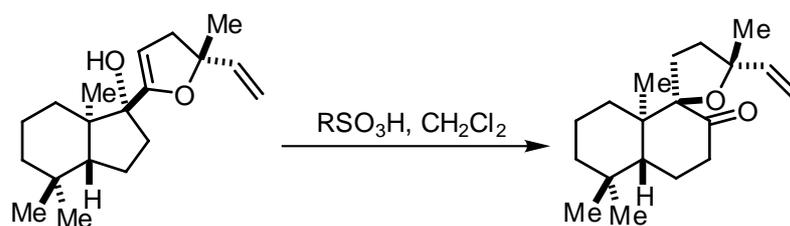
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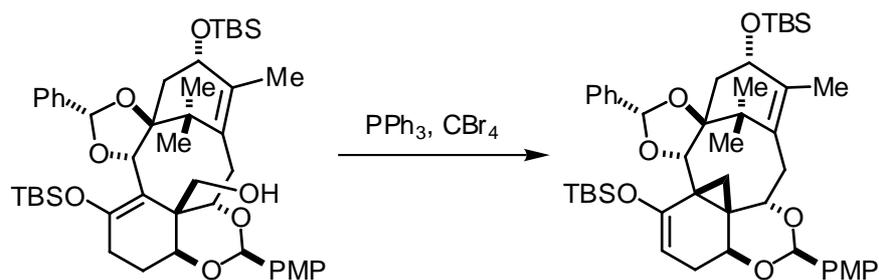
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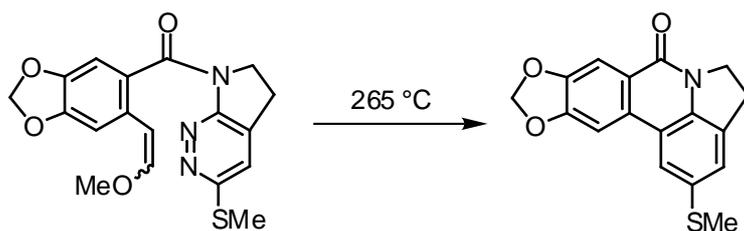
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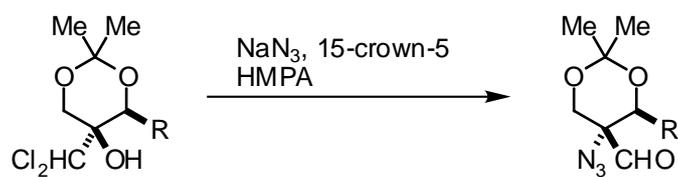
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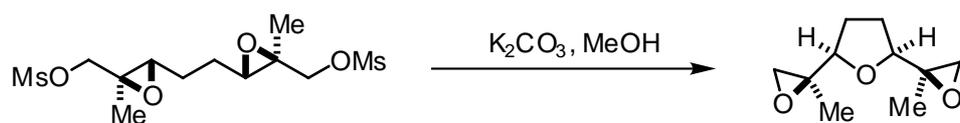
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## Exercise 23



## Exercise 24



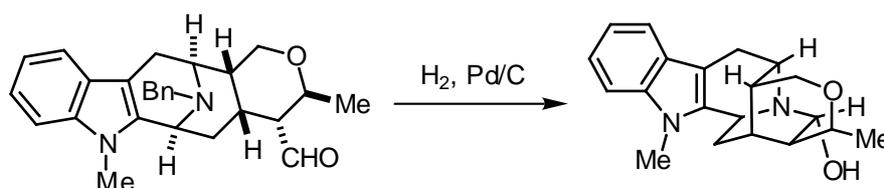


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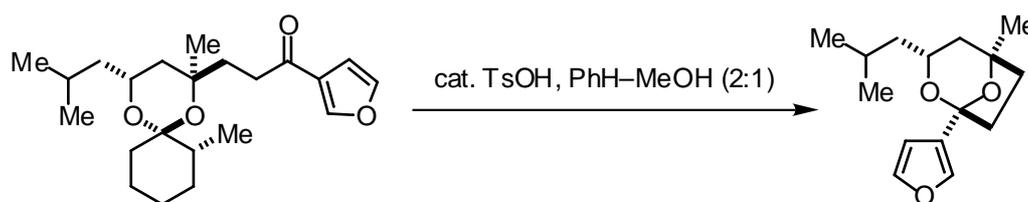
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## Additions to Aldehydes and Ketones

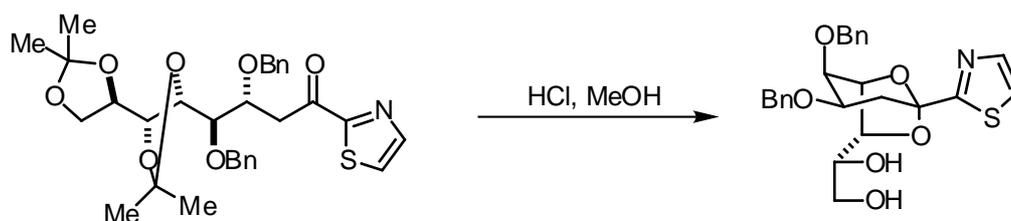
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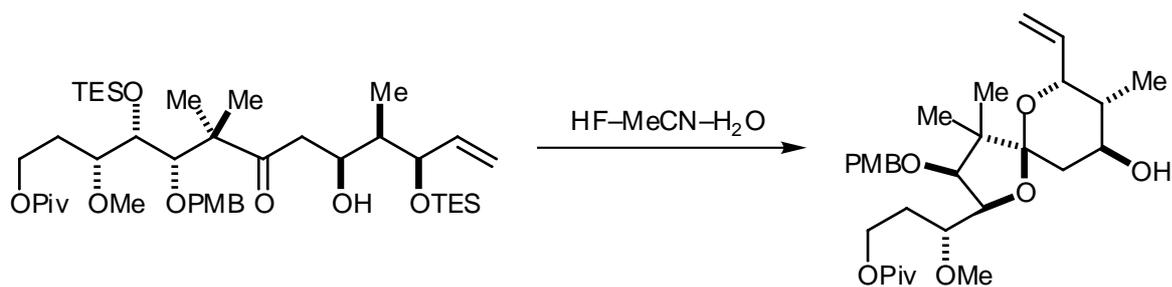
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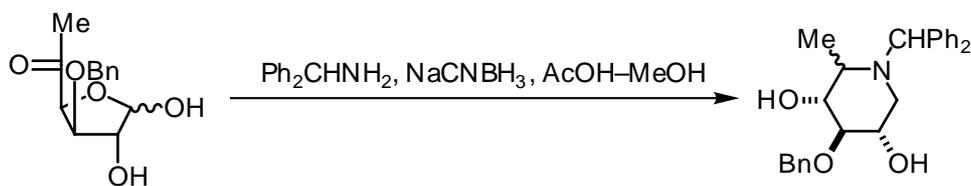
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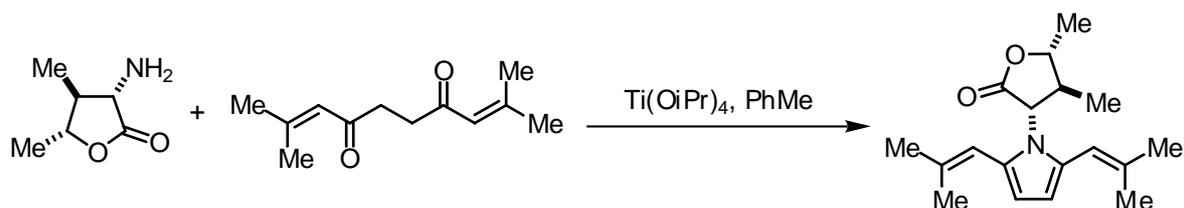
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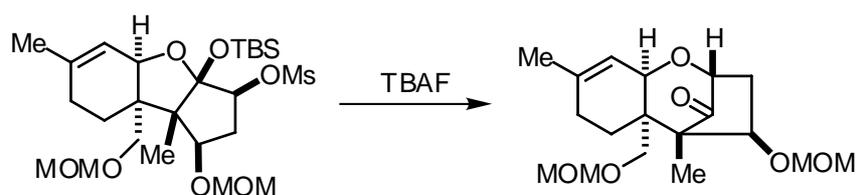
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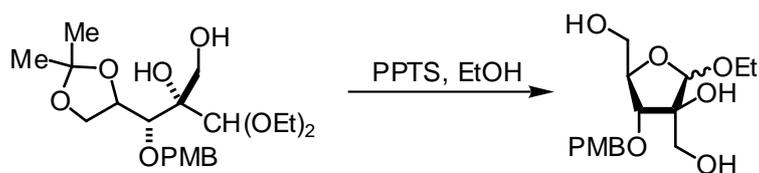
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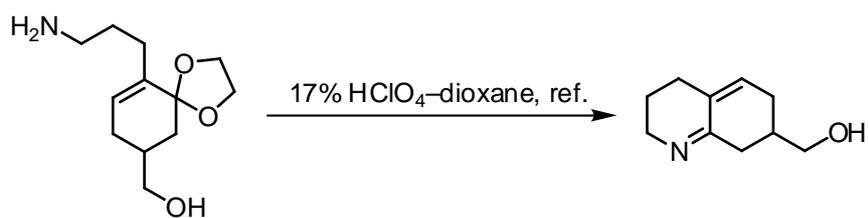
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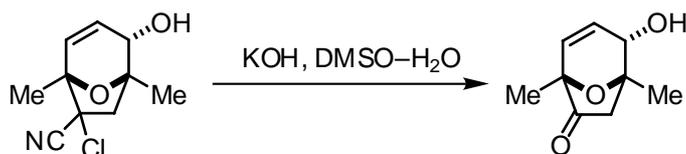
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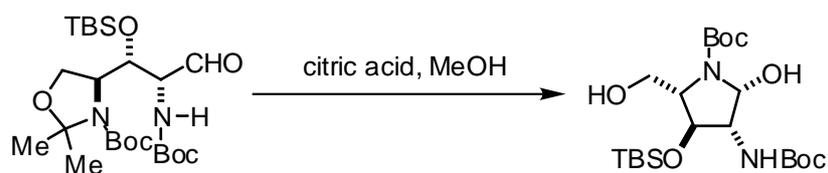
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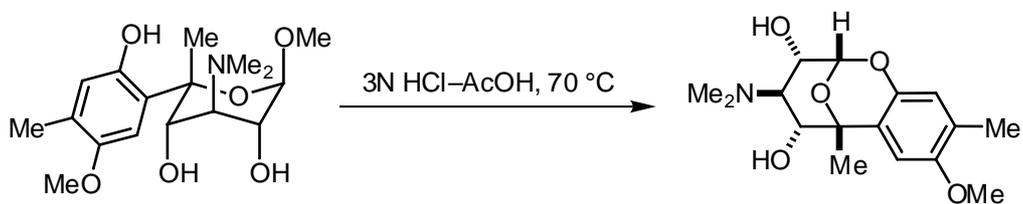
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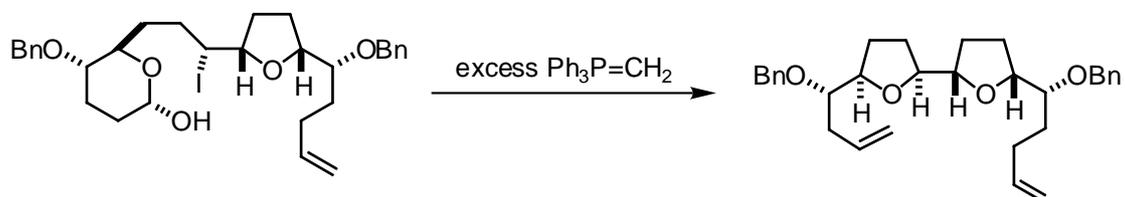
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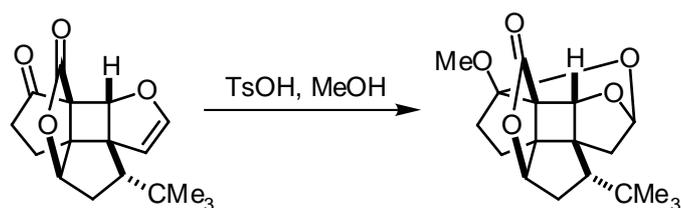
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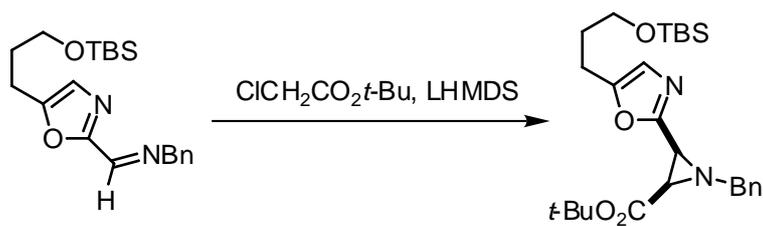
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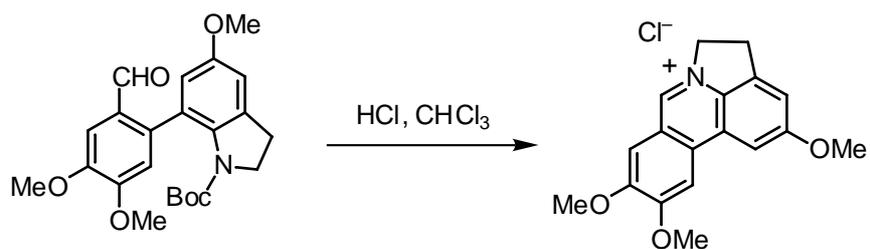
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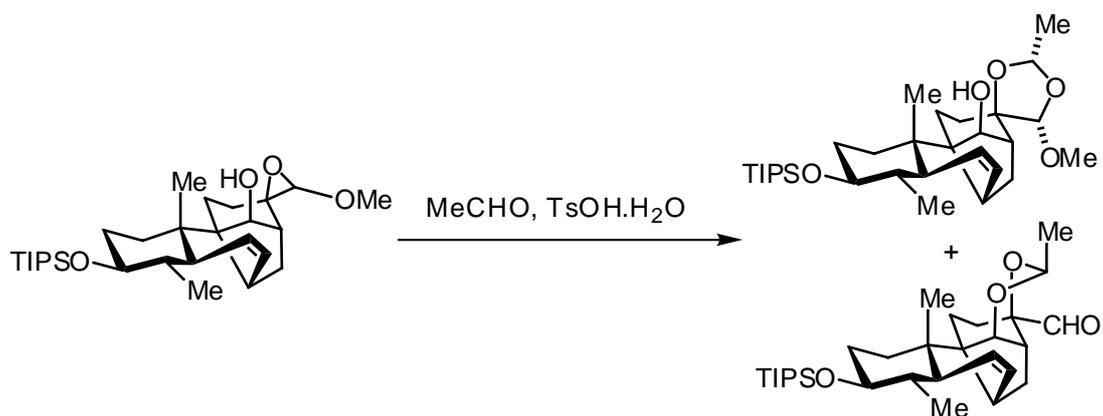
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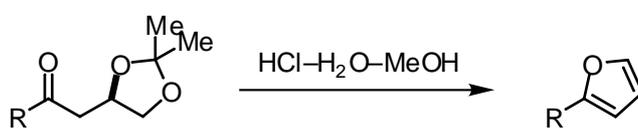
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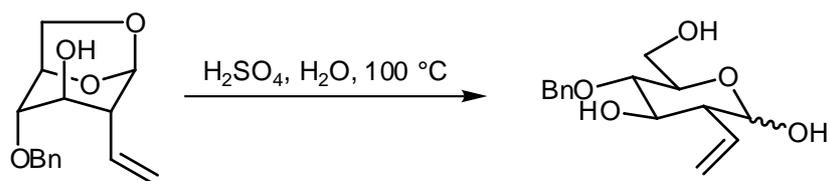
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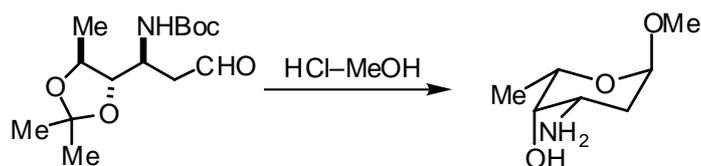
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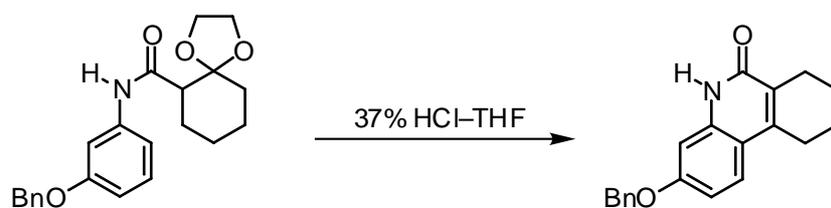
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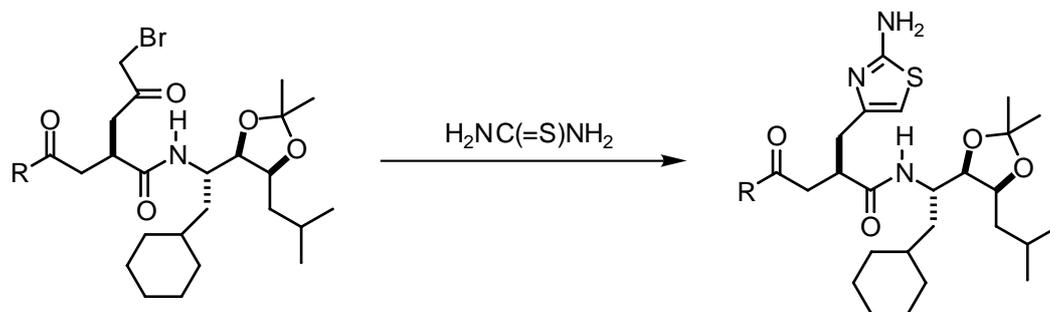
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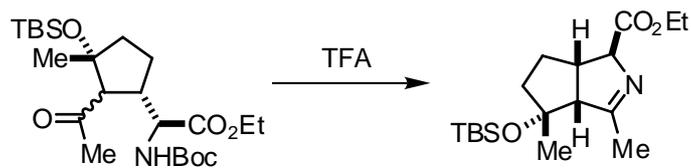
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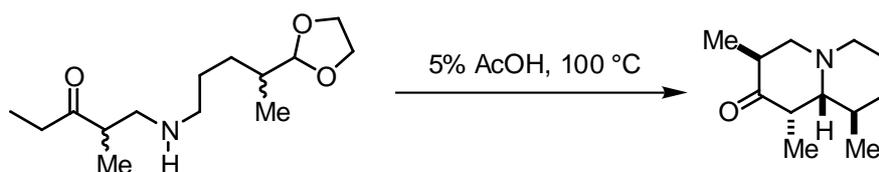
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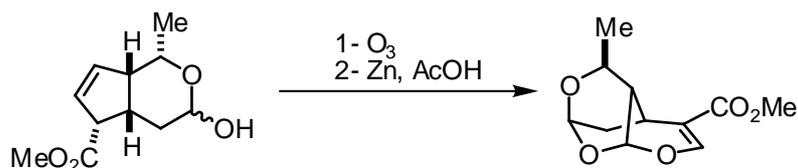
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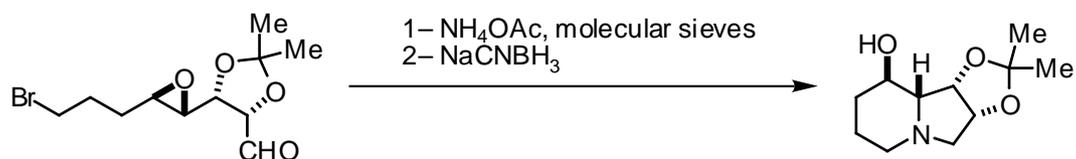
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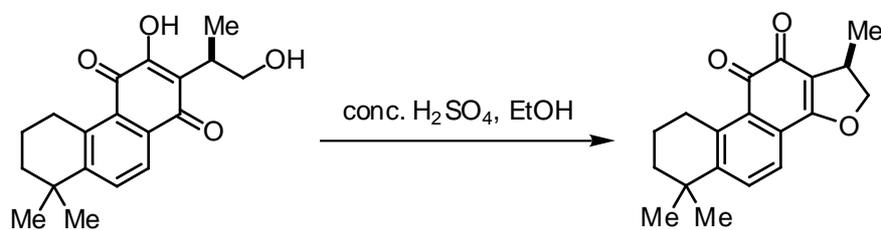
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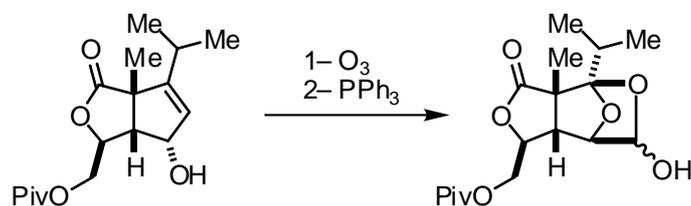
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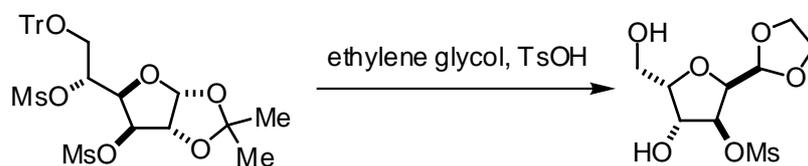
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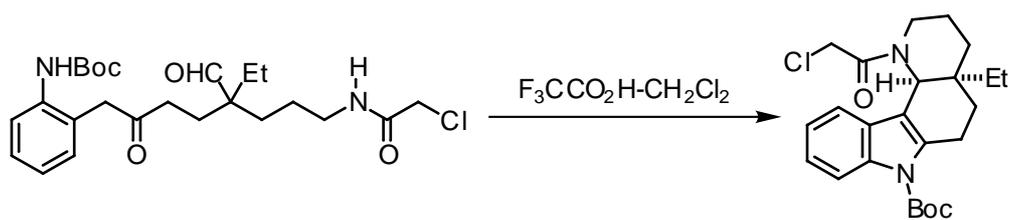
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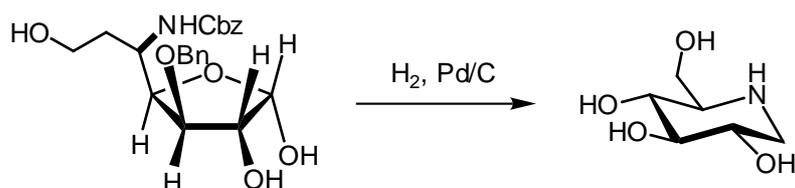
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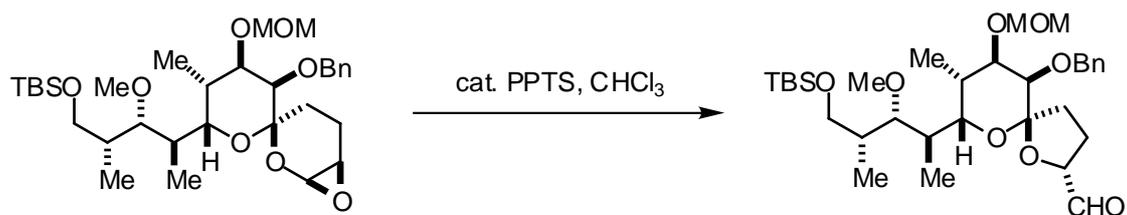
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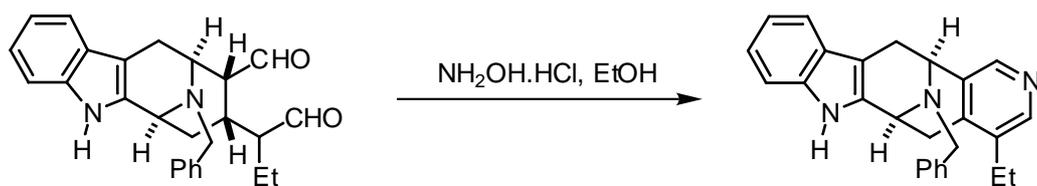
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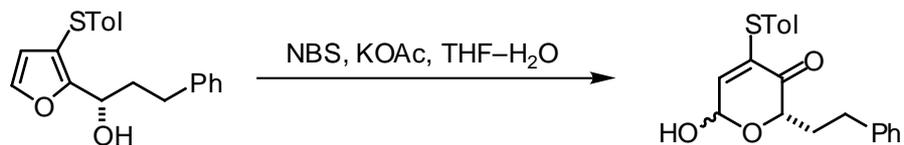
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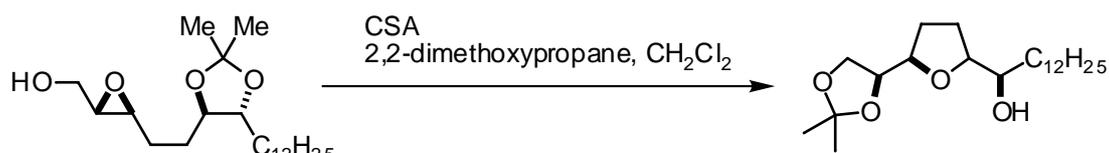
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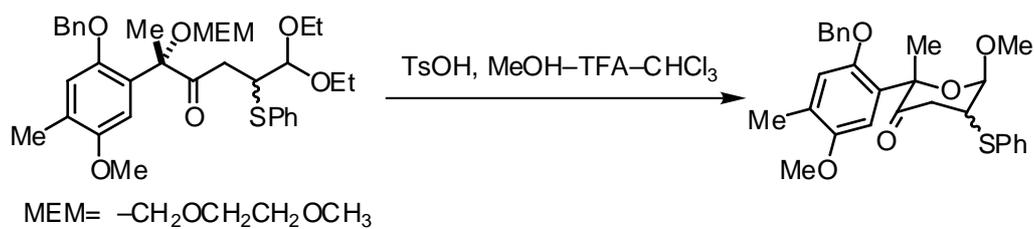
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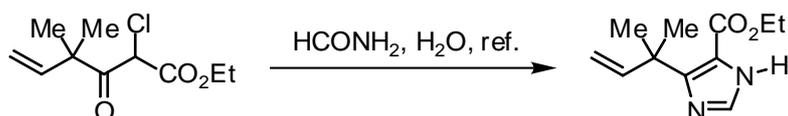
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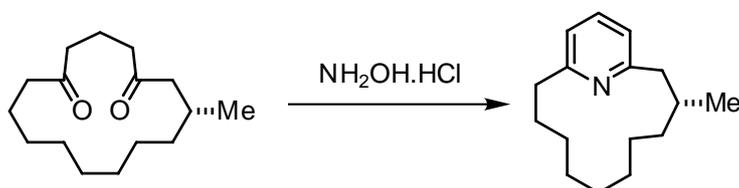
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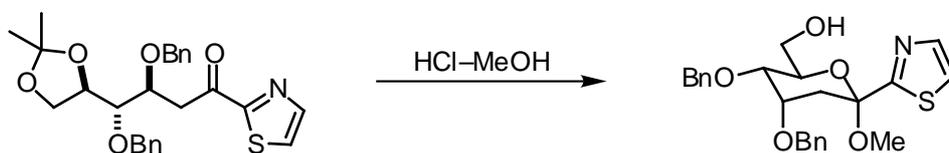
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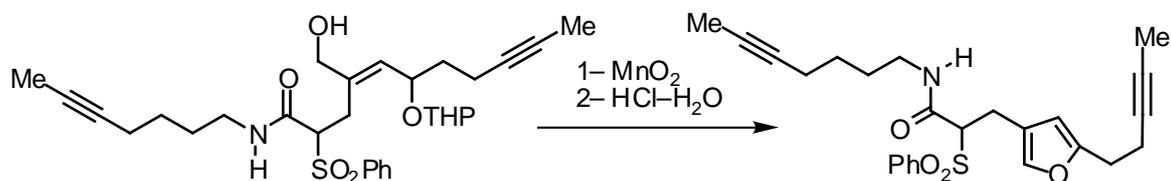
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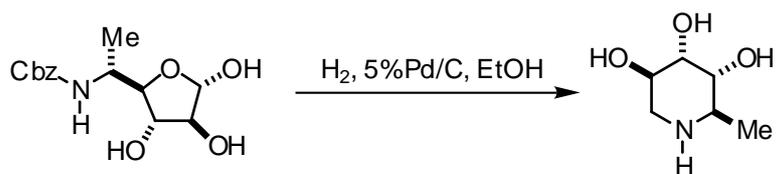
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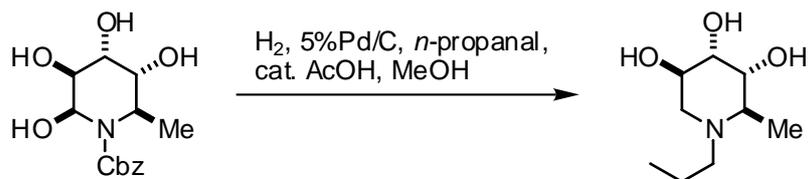
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## Exercise 65



## Exercise 66



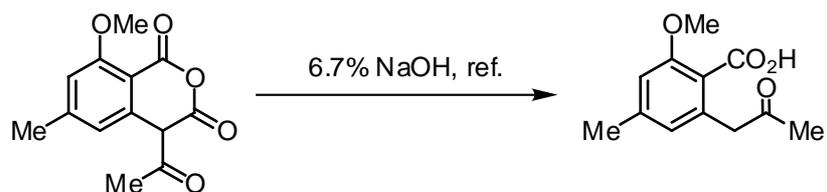


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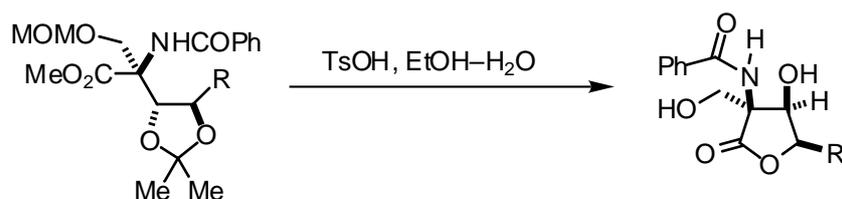
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## Derivatives of Carboxylic Acids

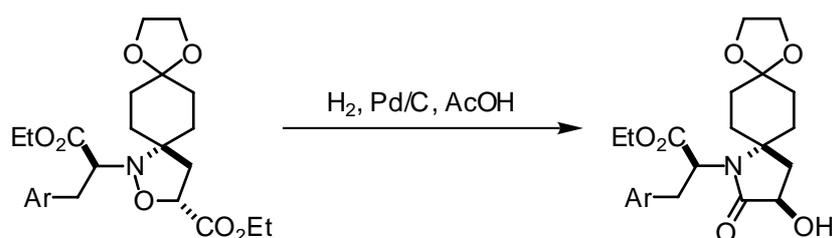
### Exercise 67



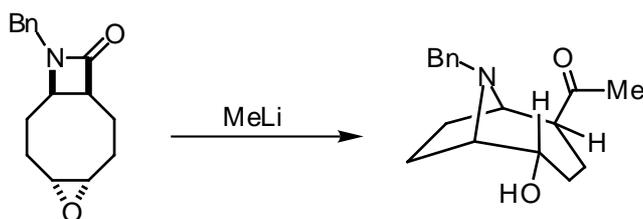
### Exercise 68



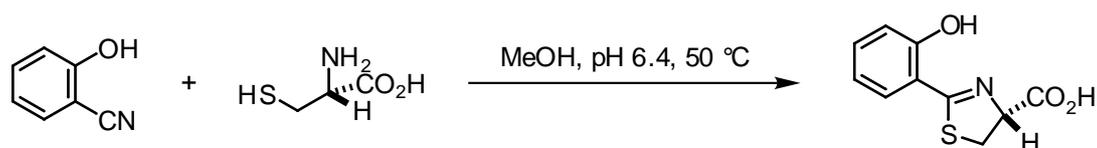
### Exercise 69



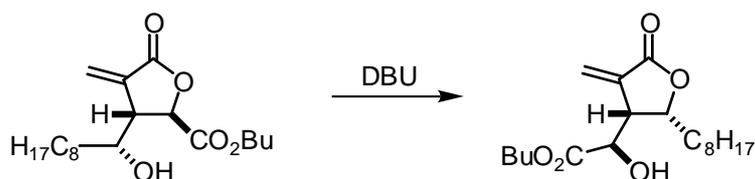
## Exercise 70



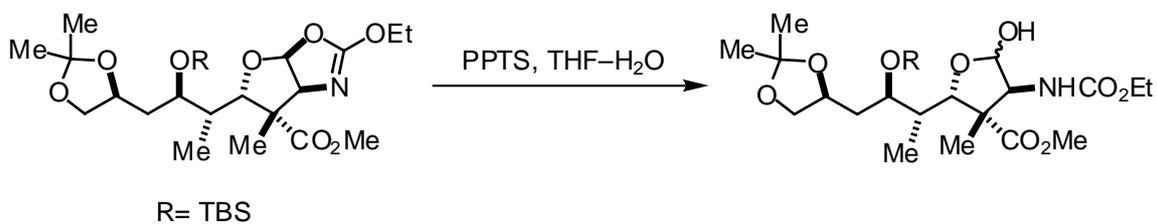
## Exercise 71



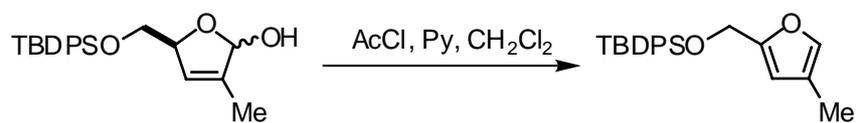
## Exercise 72



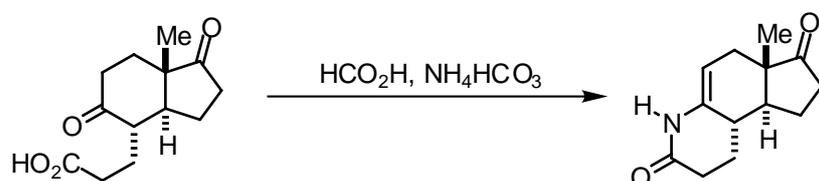
## Exercise 73



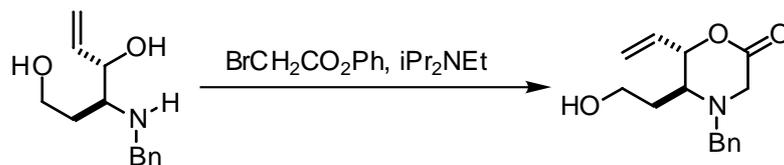
## Exercise 74



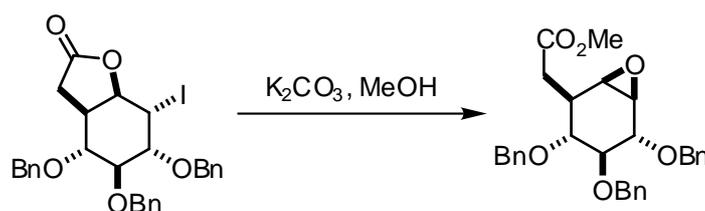
## Exercise 75



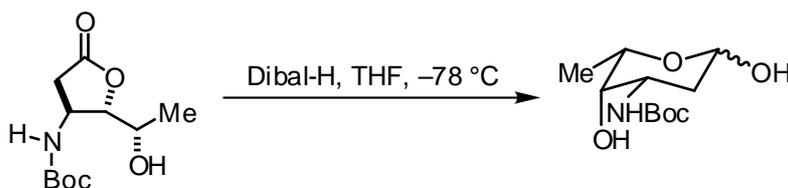
## Exercise 76



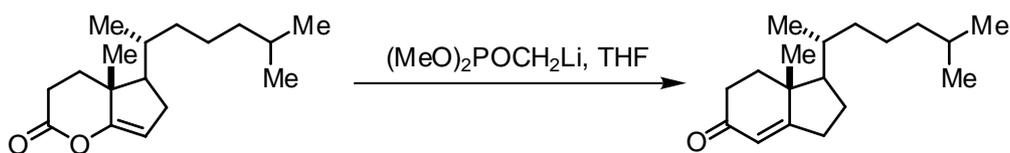
## Exercise 77



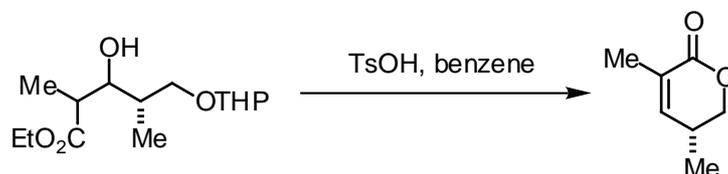
## Exercise 78



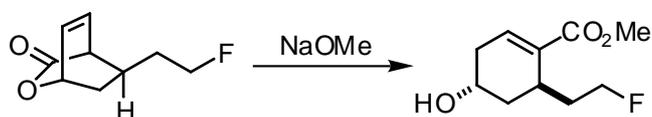
## Exercise 79



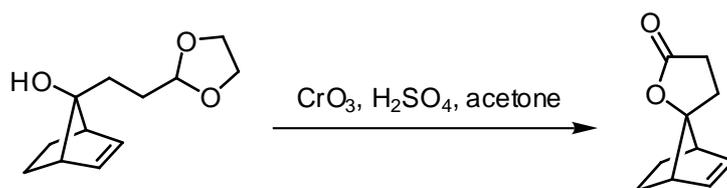
## Exercise 80



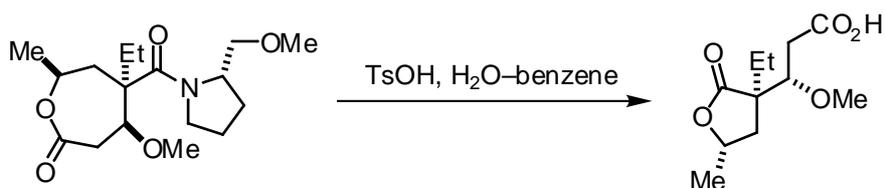
## Exercise 81



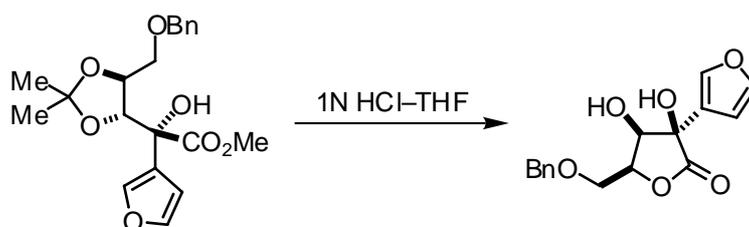
## Exercise 82



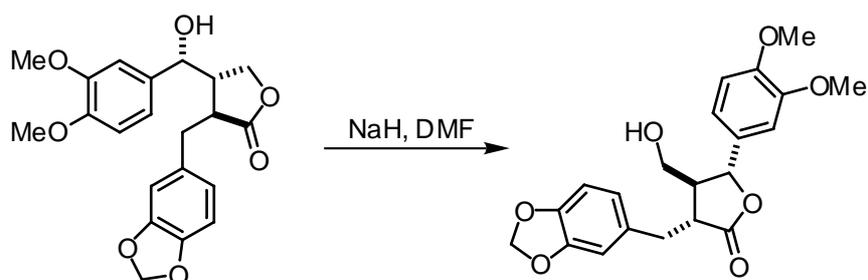
## Exercise 83



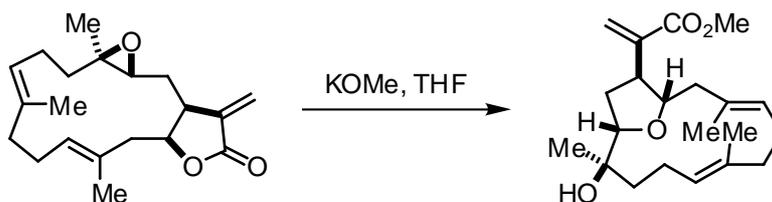
## Exercise 84



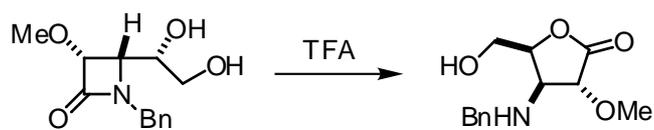
## Exercise 85



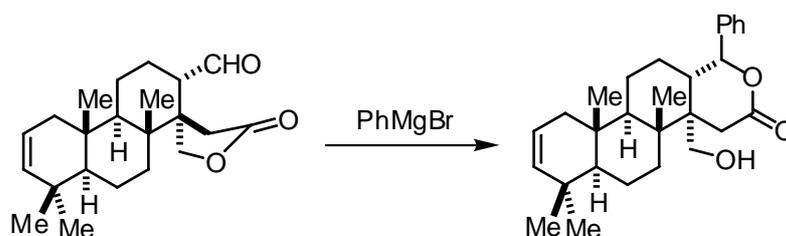
## Exercise 86



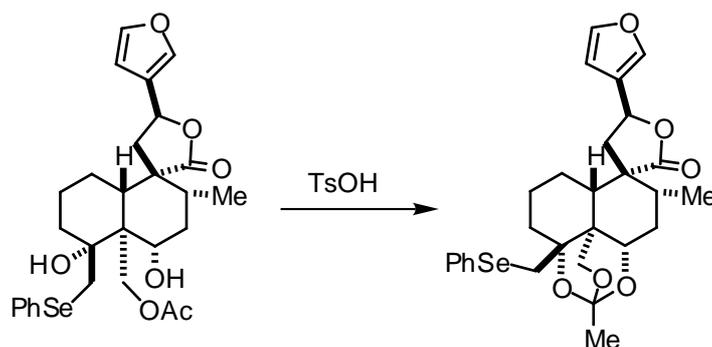
## Exercise 87



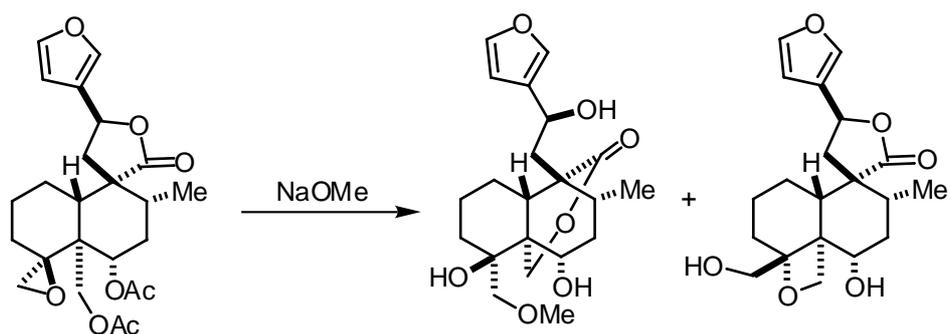
## Exercise 88



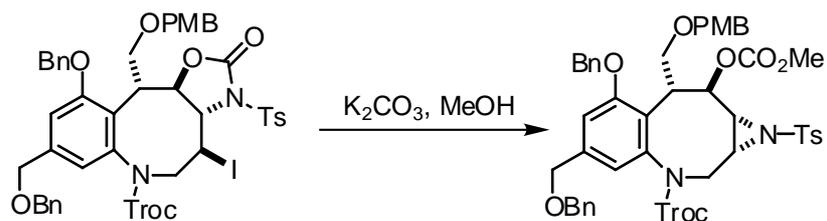
## Exercise 89



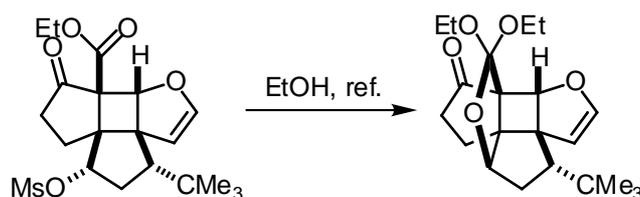
## Exercise 90



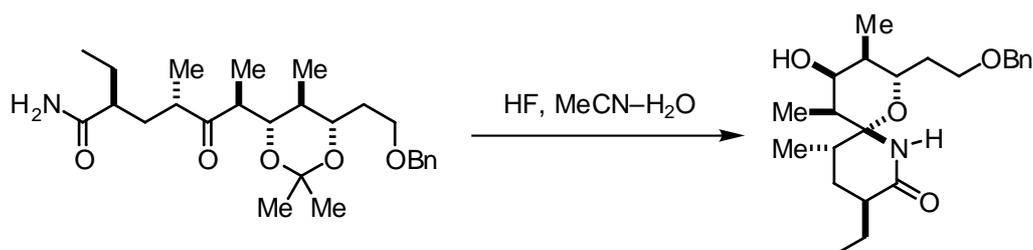
## Exercise 91



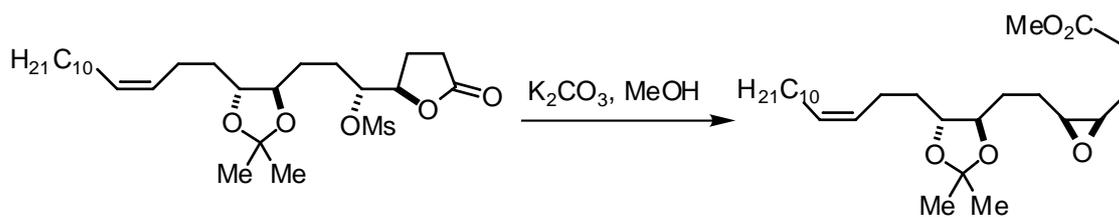
## Exercise 92



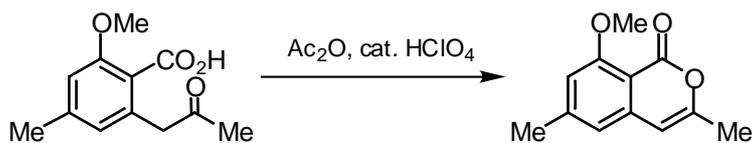
## Exercise 93



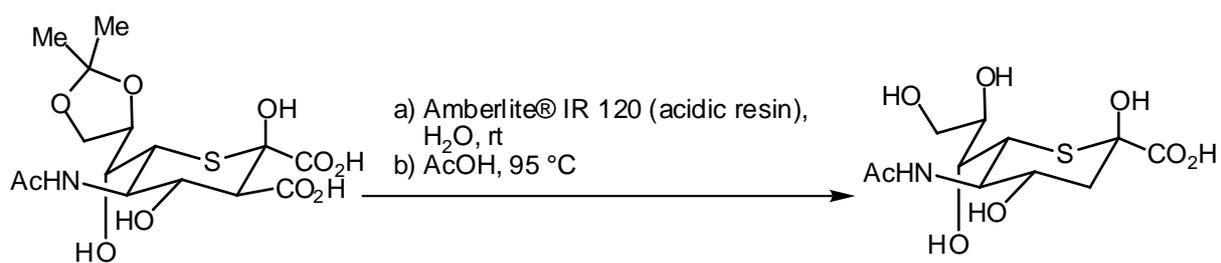
## Exercise 94



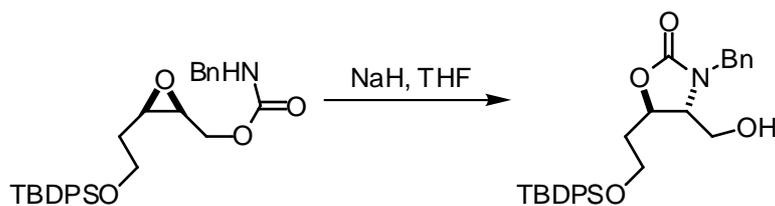
## Exercise 95



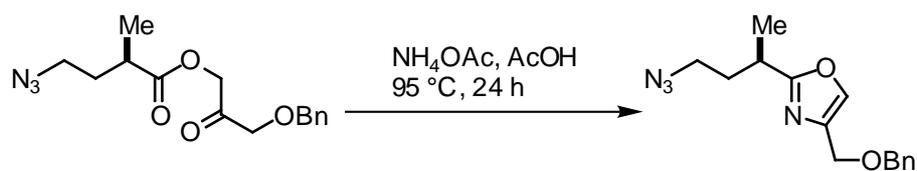
## Exercise 96



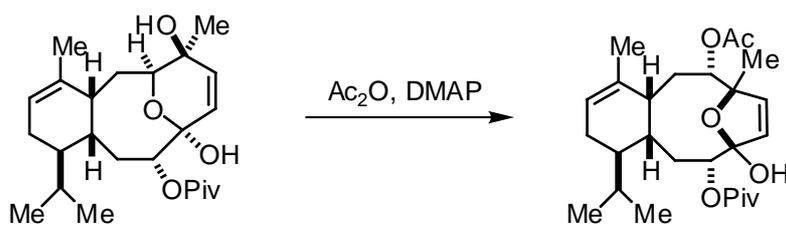
## Exercise 97



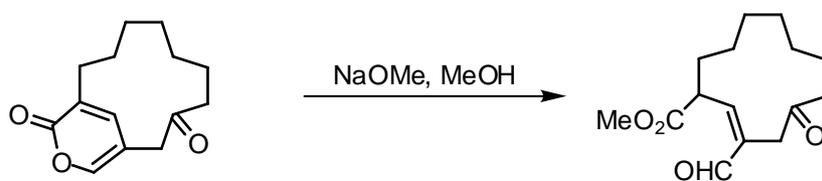
## Exercise 98



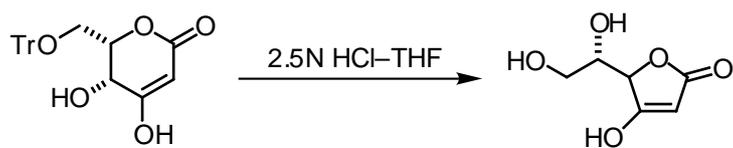
## Exercise 99



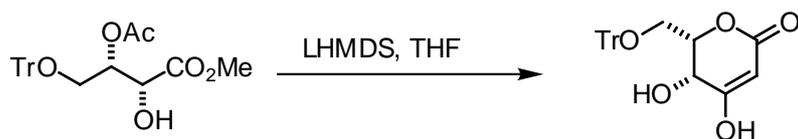
## Exercise 100



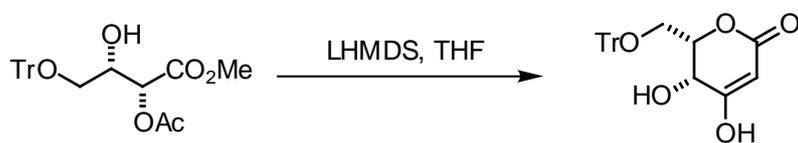
## Exercise 101



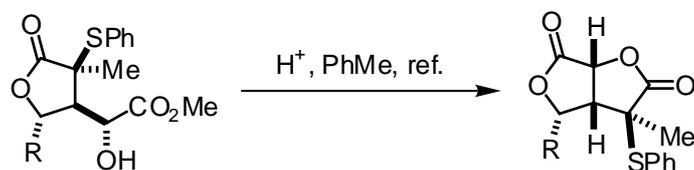
## Exercise 102



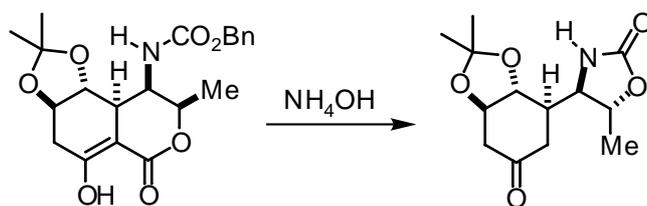
## Exercise 103



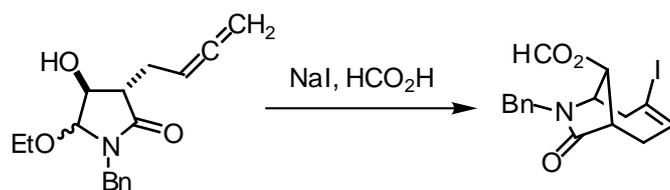
## Exercise 104



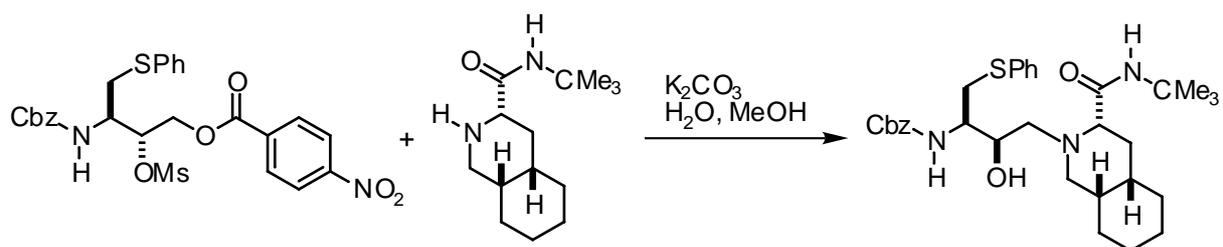
## Exercise 105



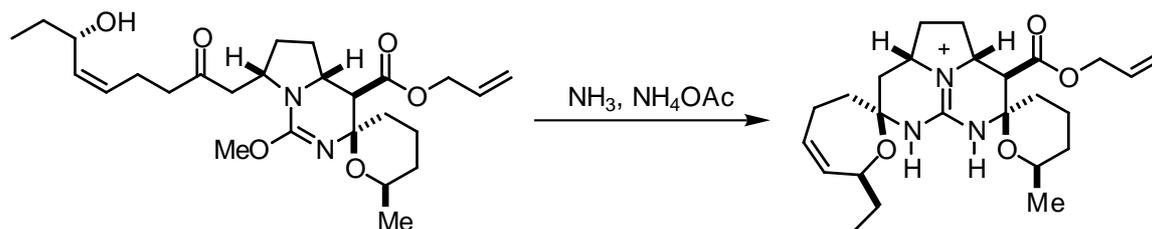
## Exercise 106



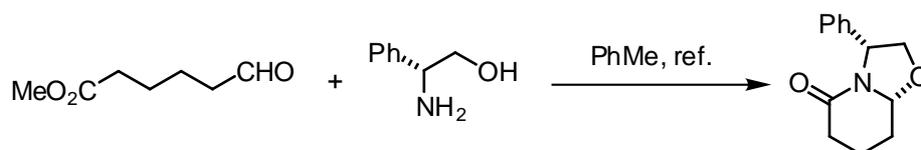
## Exercise 107



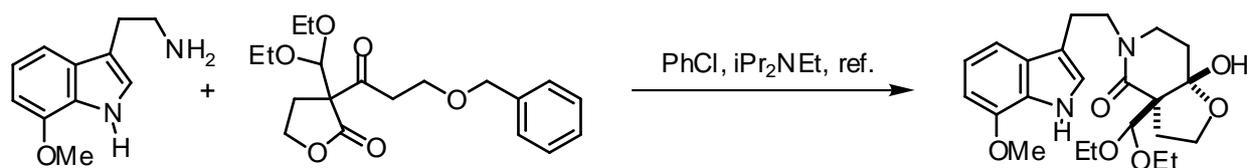
## Exercise 108



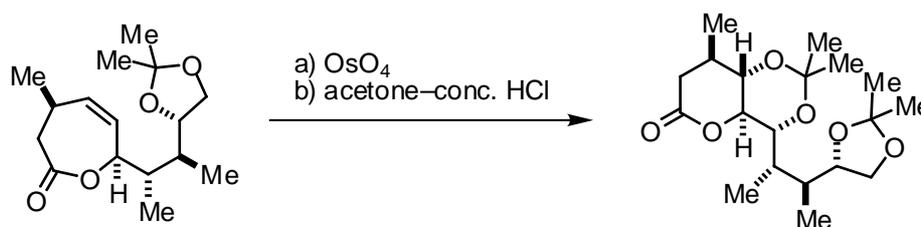
## Exercise 109



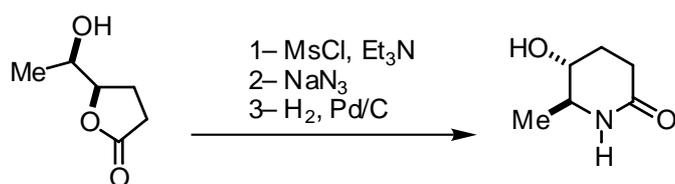
## Exercise 110



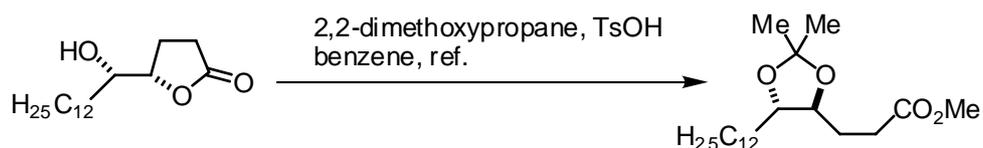
## Exercise 111



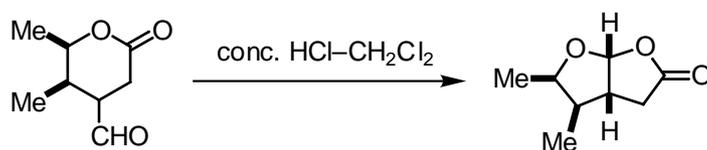
## Exercise 112



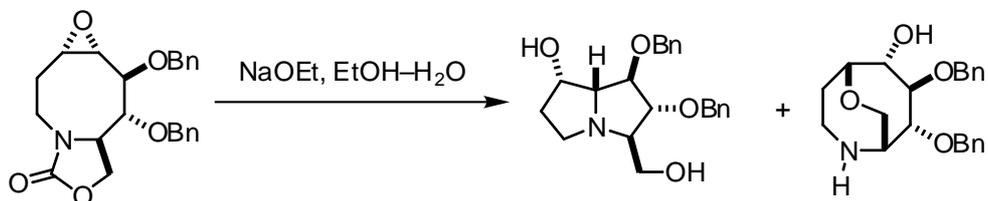
## Exercise 113



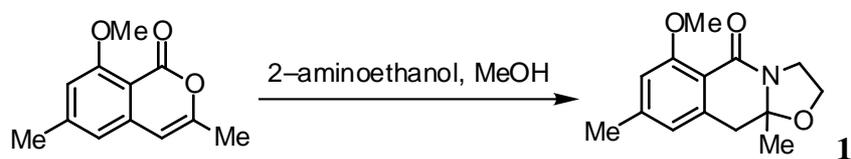
## Exercise 114



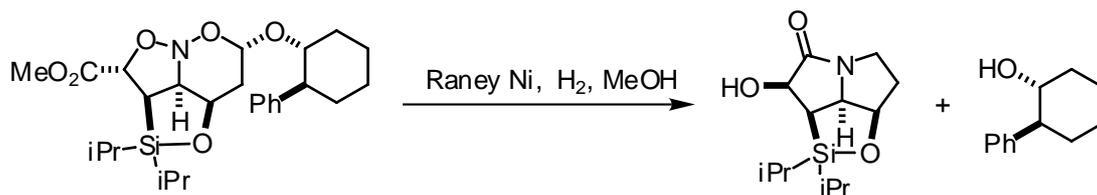
## Exercise 115



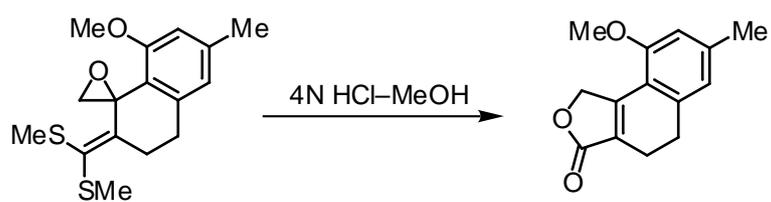
## Exercise 116



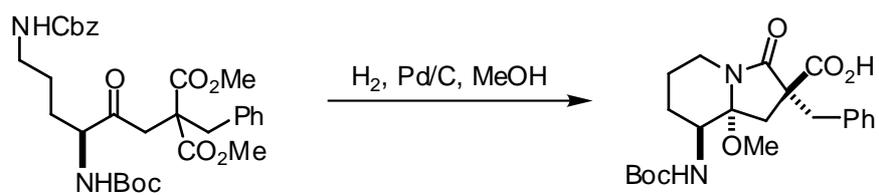
## Exercise 117



## Exercise 118



## Exercise 119



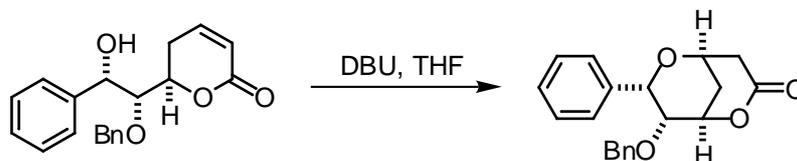


# Chapter 4

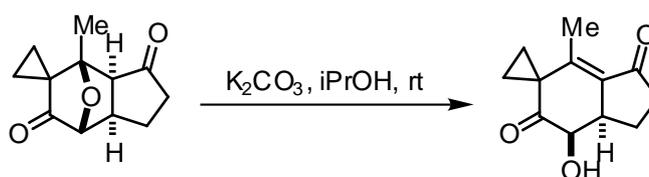
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## Conjugated Additions to Electron-Deficient Alkenes

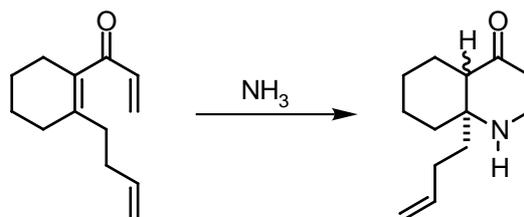
### Exercise 120



### Exercise 121

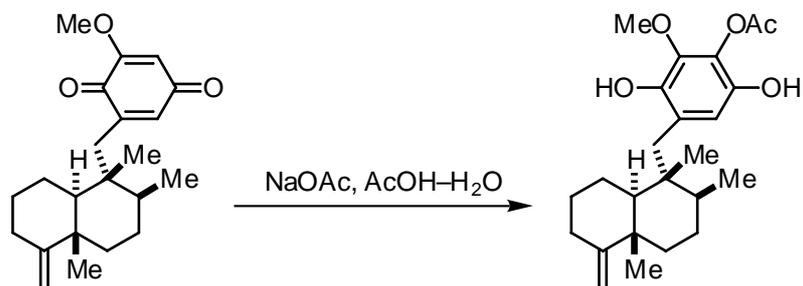


### Exercise 122

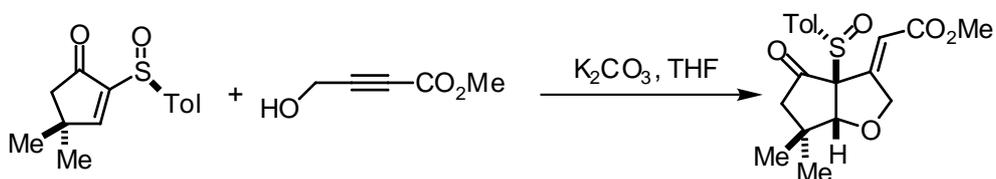




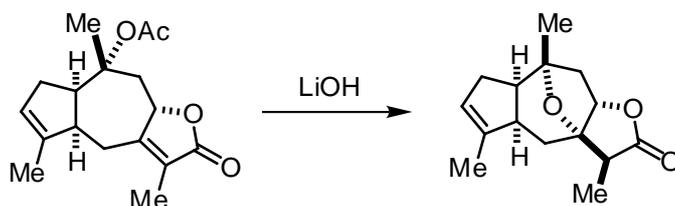
## Exercise 129



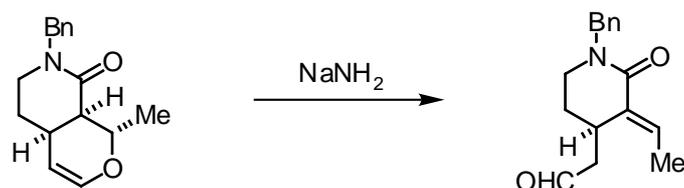
## Exercise 130



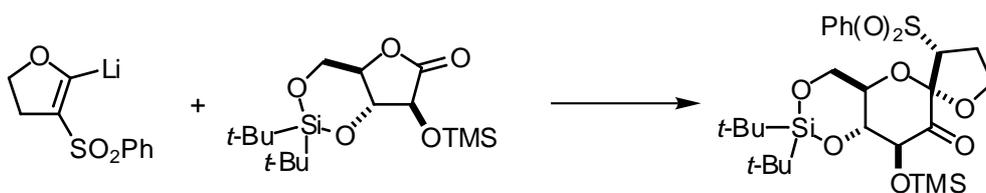
## Exercise 131



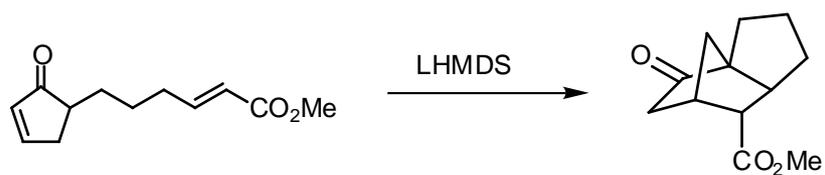
## Exercise 132



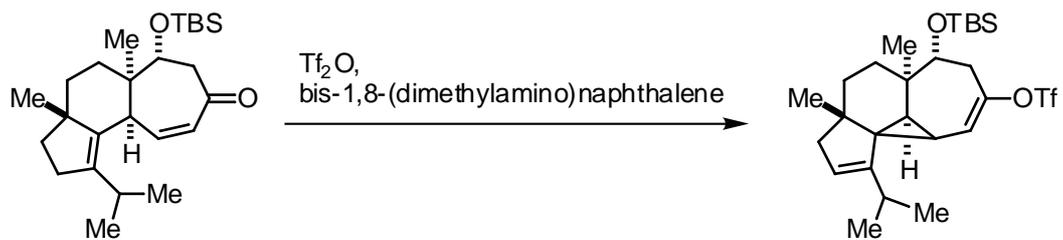
## Exercise 133



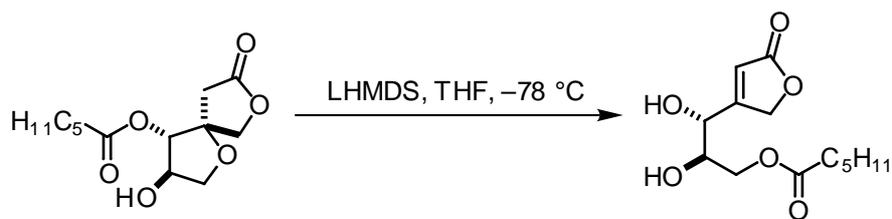
## Exercise 134



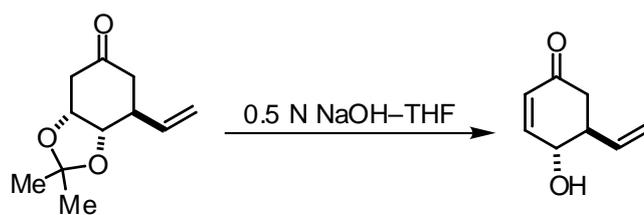
## Exercise 135



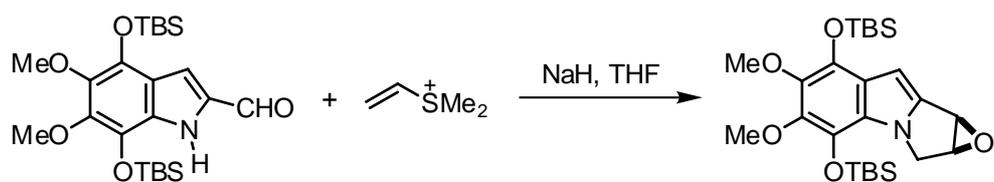
## Exercise 136



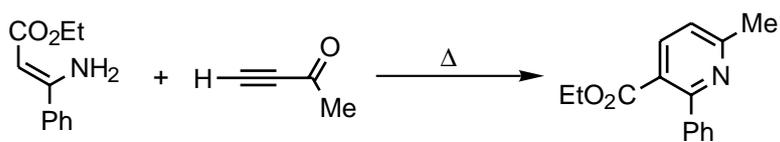
## Exercise 137



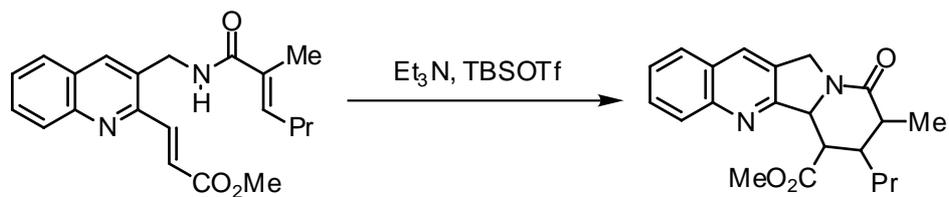
## Exercise 138



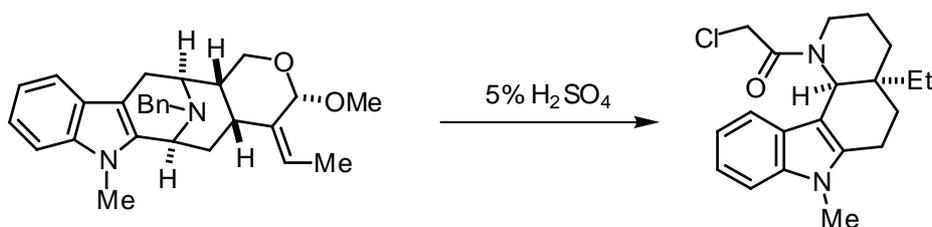
## Exercise 139



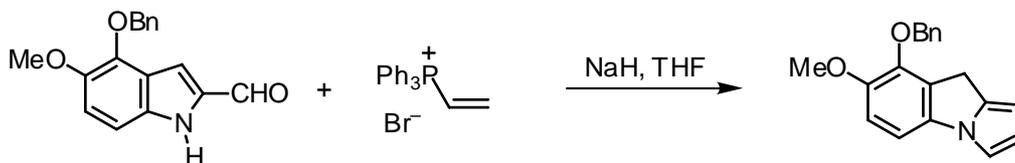
## Exercise 140



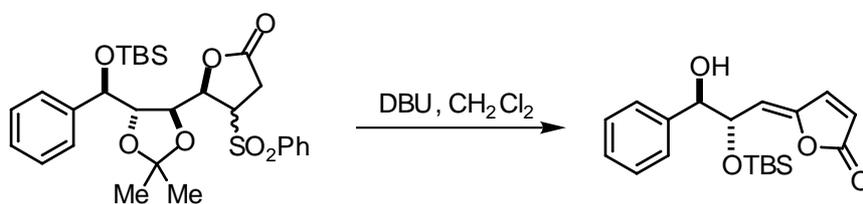
## Exercise 141



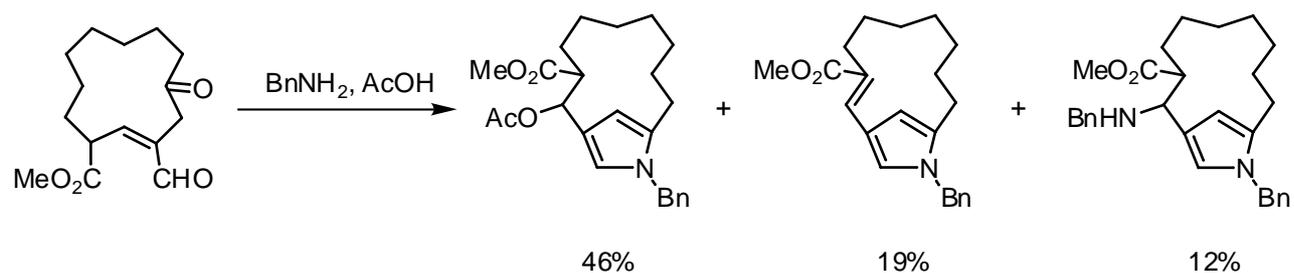
## Exercise 142



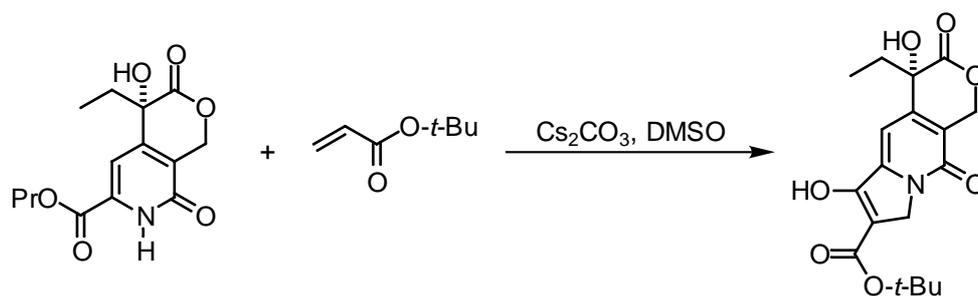
## Exercise 143



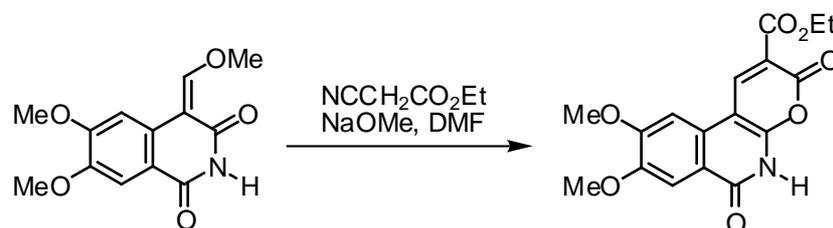
## Exercise 144



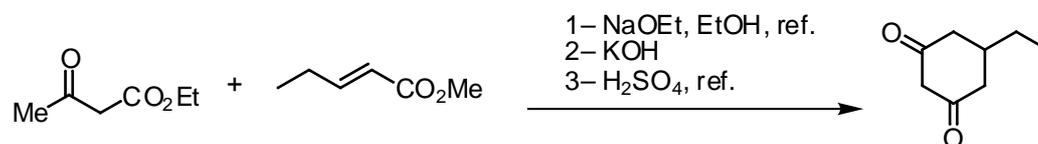
## Exercise 145



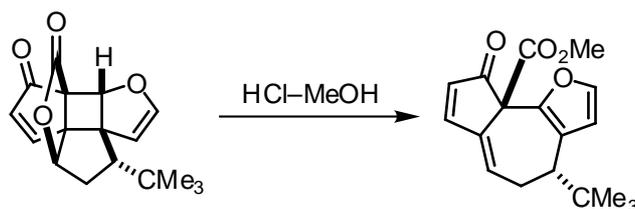
## Exercise 146



## Exercise 147



## Exercise 148



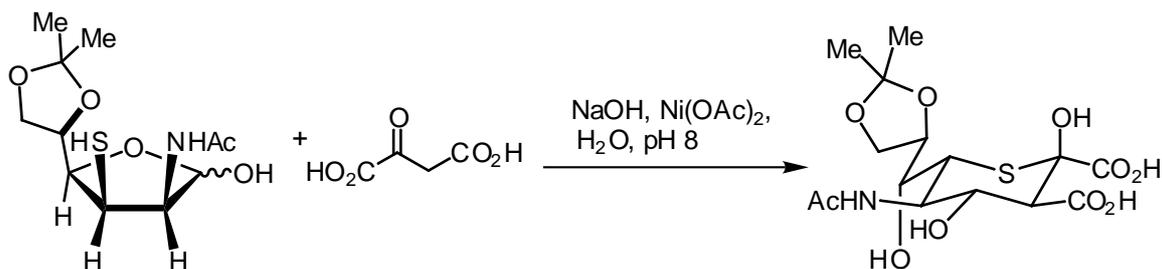




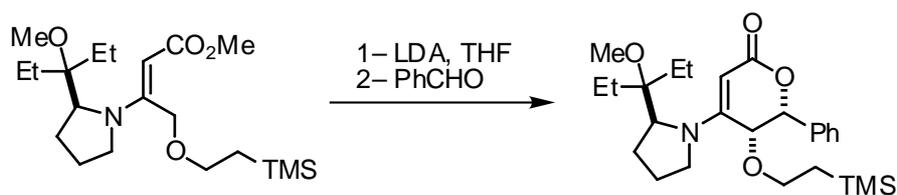
# Chapter 5

## Reactions via Enols and Enolates

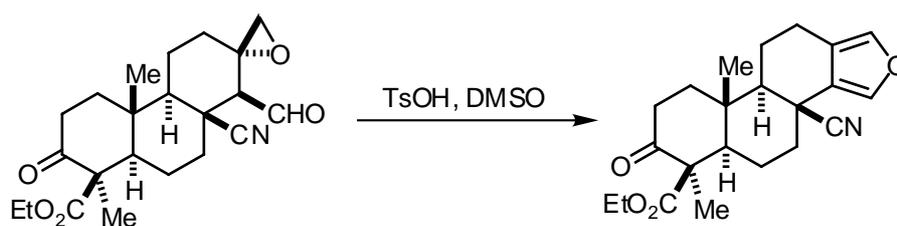
### Exercise 150



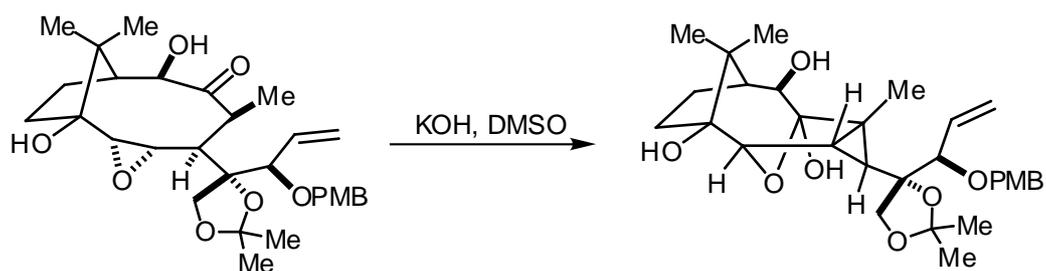
### Exercise 151



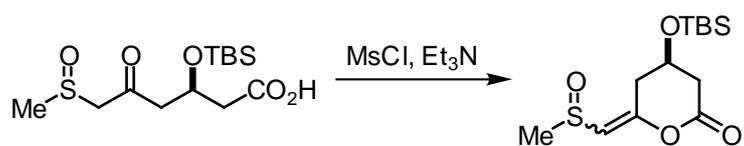
### Exercise 152



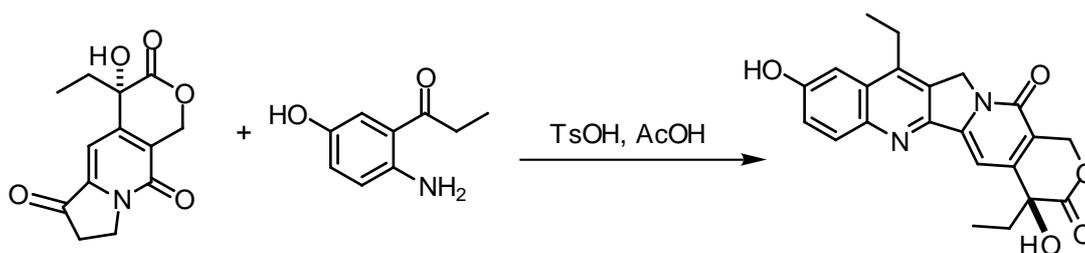
## Exercise 153



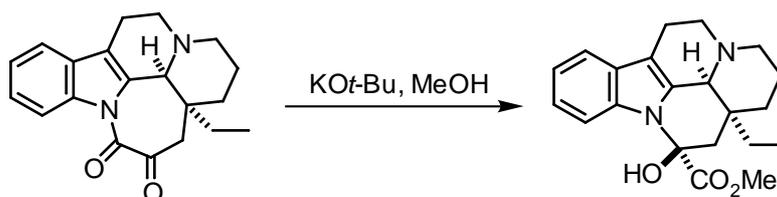
## Exercise 154



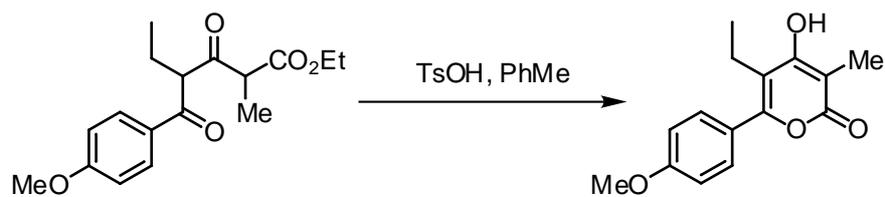
## Exercise 155



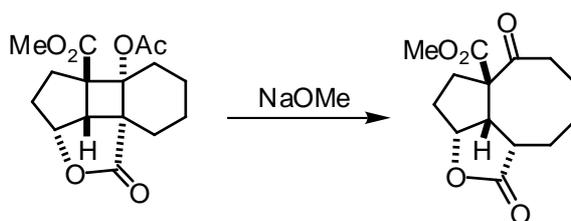
## Exercise 156



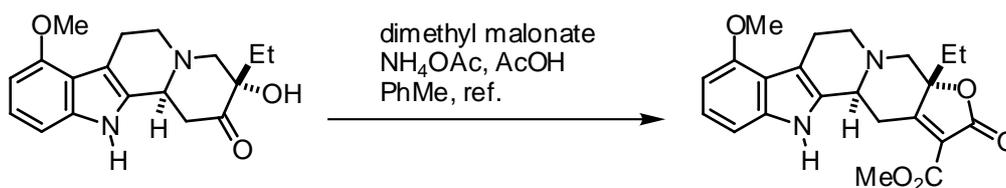
## Exercise 157



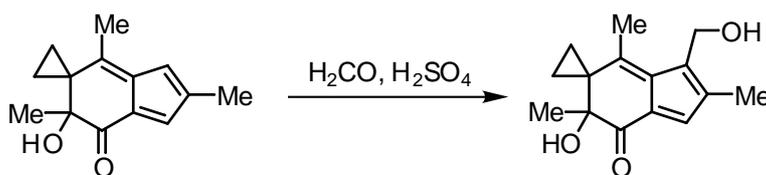
## Exercise 158



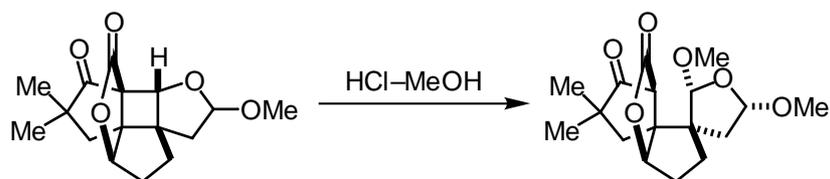
## Exercise 159



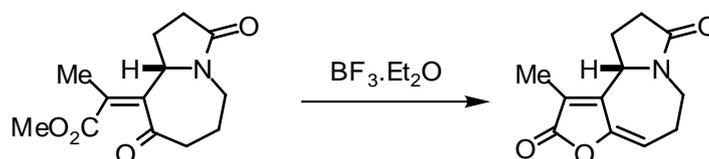
## Exercise 160



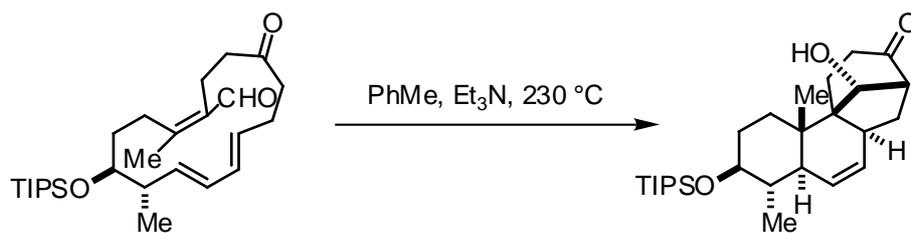
## Exercise 161



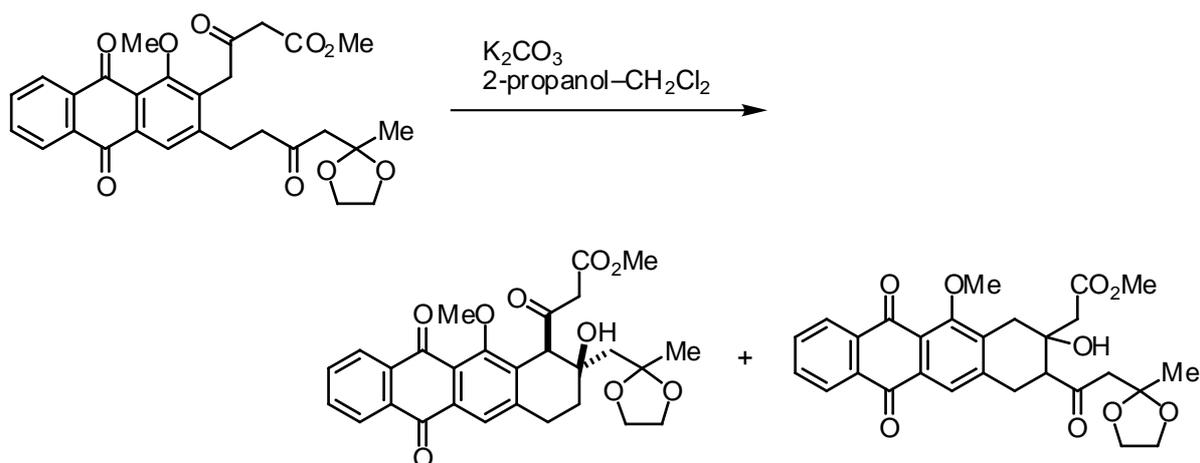
## Exercise 162



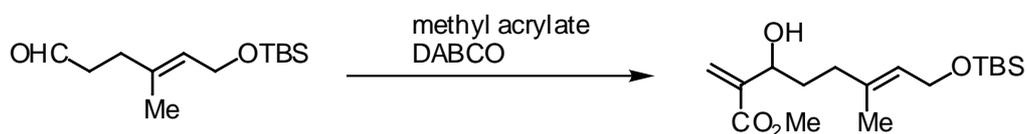
## Exercise 163



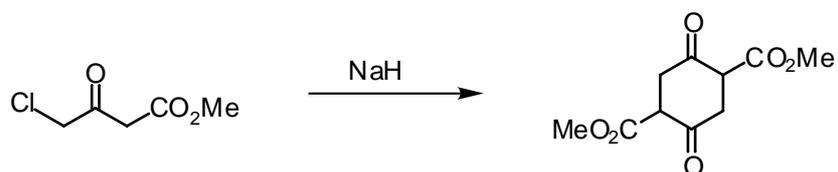
## Exercise 164



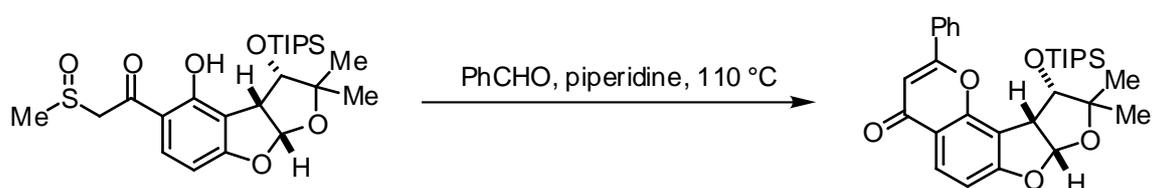
## Exercise 165



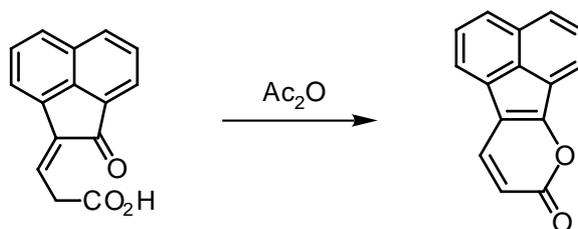
## Exercise 166



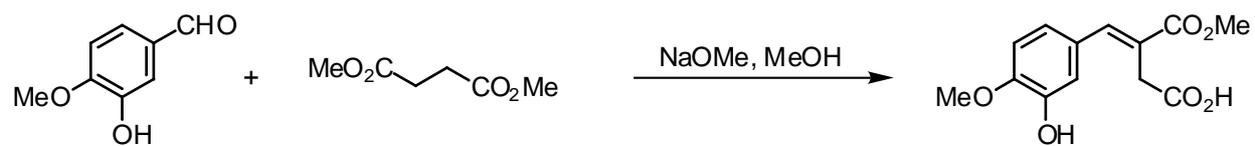
## Exercise 167



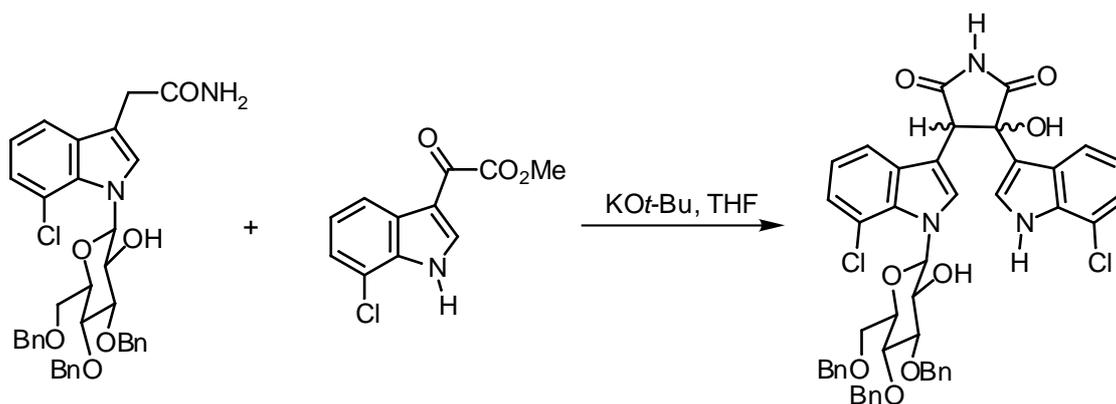
## Exercise 168



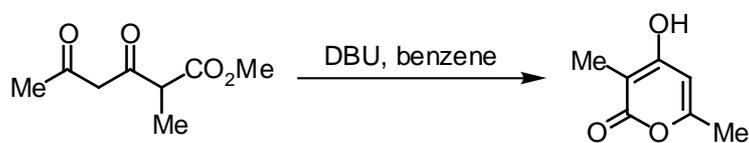
## Exercise 169



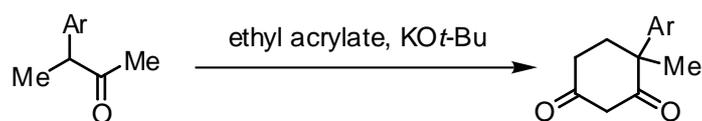
## Exercise 170



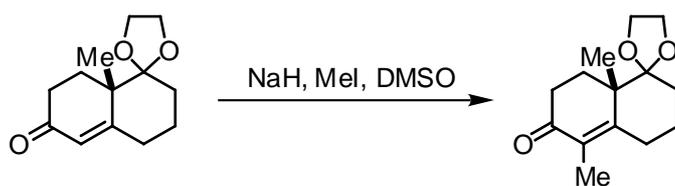
## Exercise 171



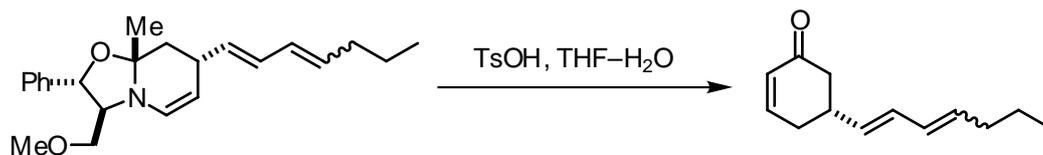
## Exercise 172



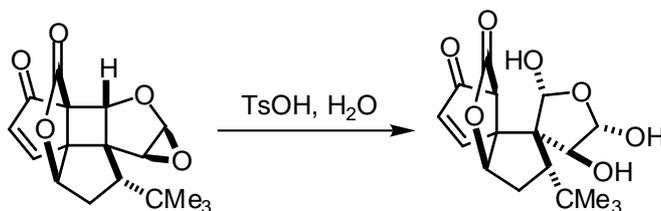
## Exercise 173



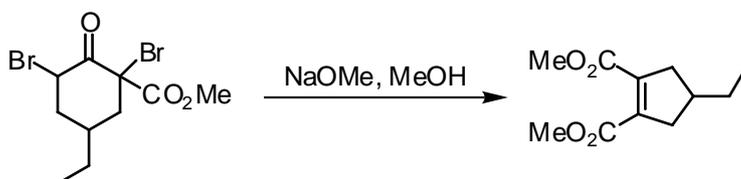
## Exercise 174



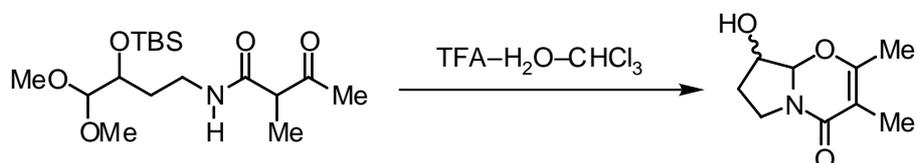
## Exercise 175



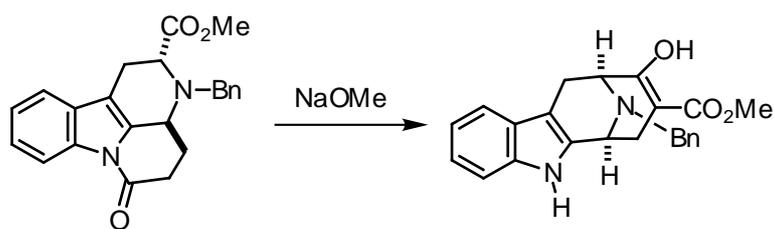
## Exercise 176



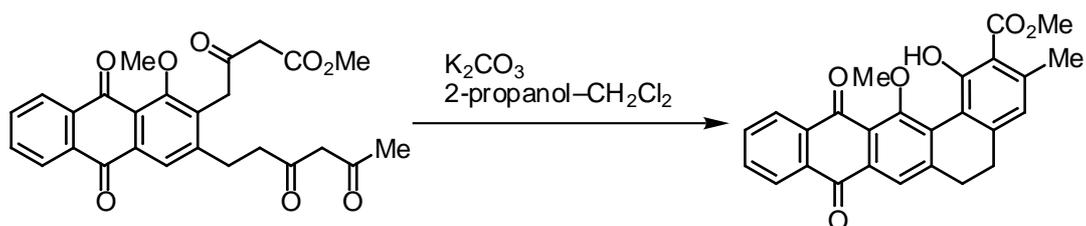
## Exercise 177



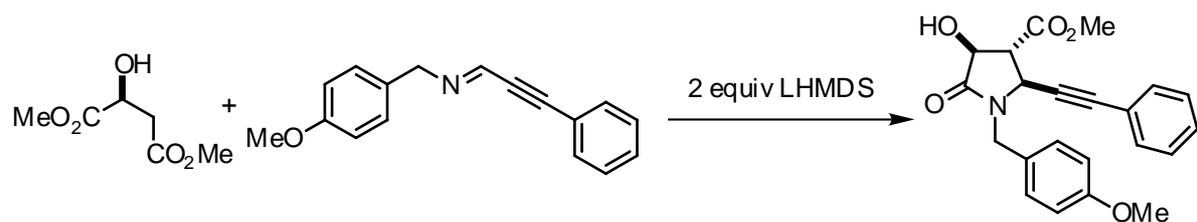
## Exercise 178



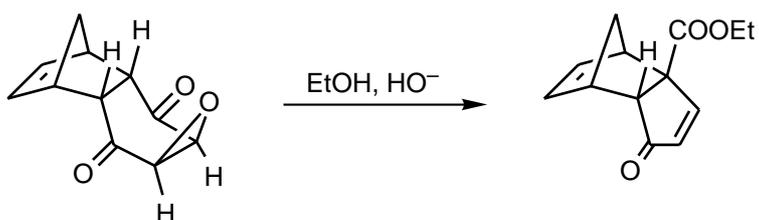
## Exercise 179



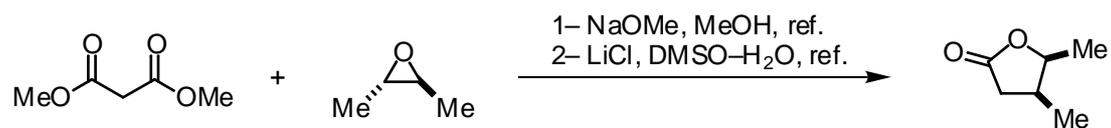
## Exercise 180



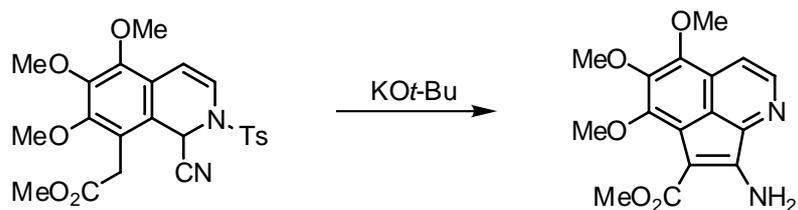
## Exercise 181



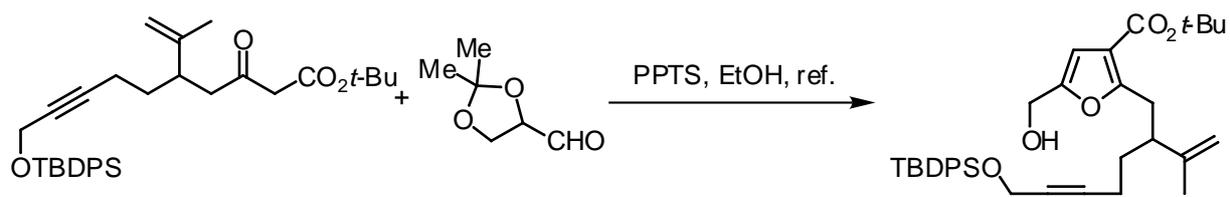
## Exercise 182



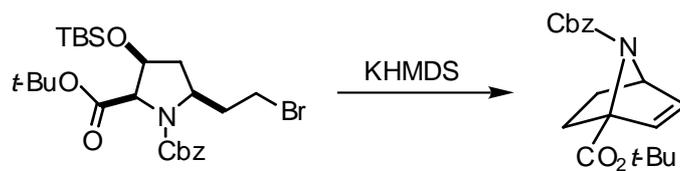
## Exercise 183



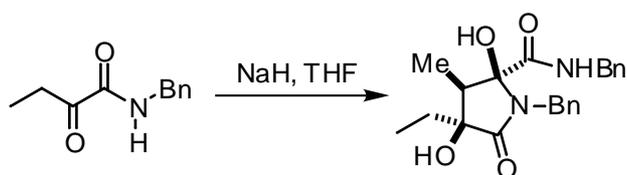
## Exercise 184



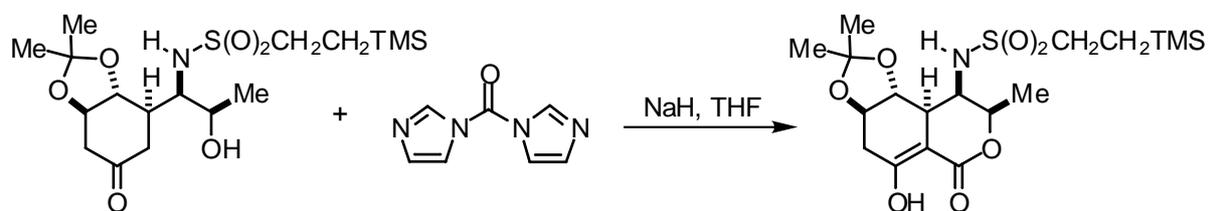
## Exercise 185



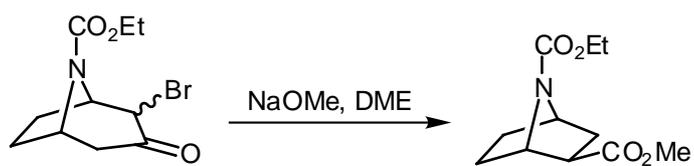
## Exercise 186



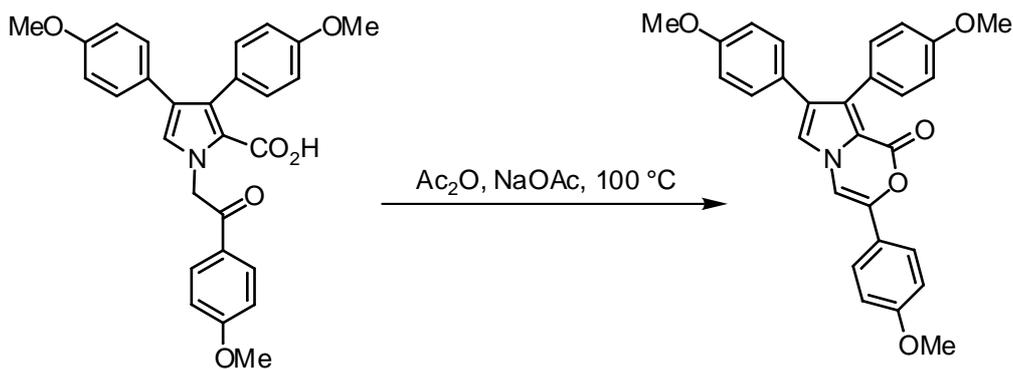
## Exercise 187



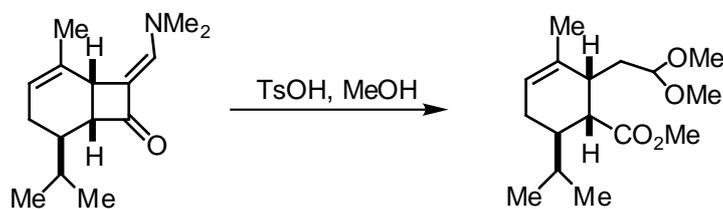
## Exercise 188



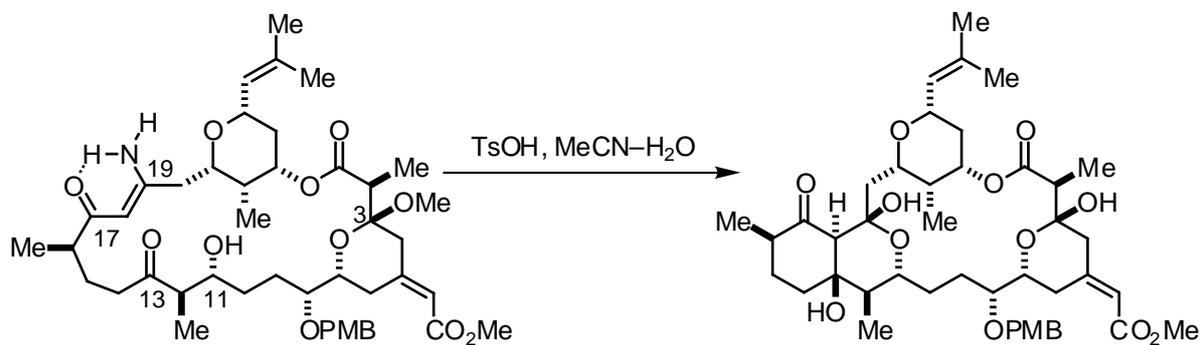
## Exercise 189



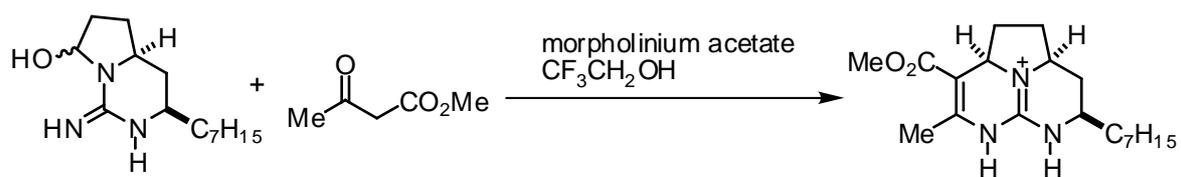
## Exercise 190



## Exercise 191



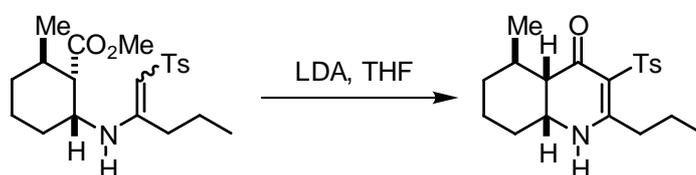
## Exercise 192



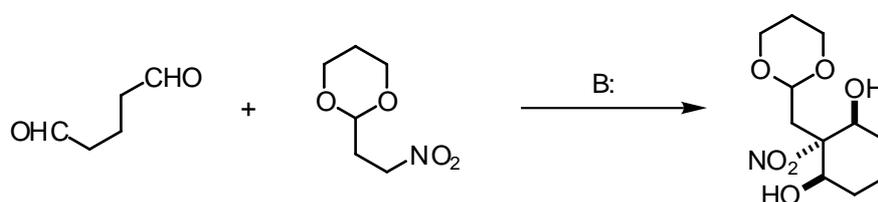
# Chapter 6

## Reactions via Carbanions Stabilized by Functional Groups Other than Carbonyl

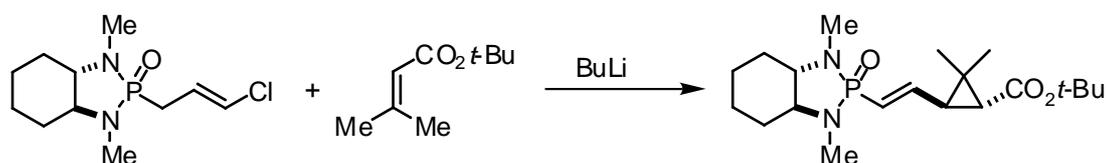
### Exercise 193



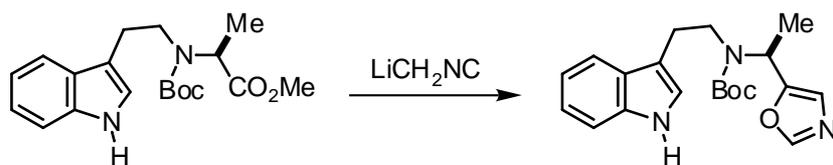
### Exercise 194



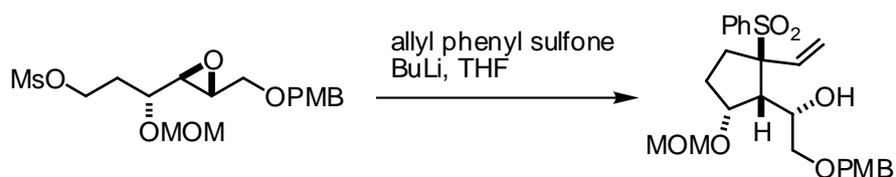
### Exercise 195



## Exercise 196



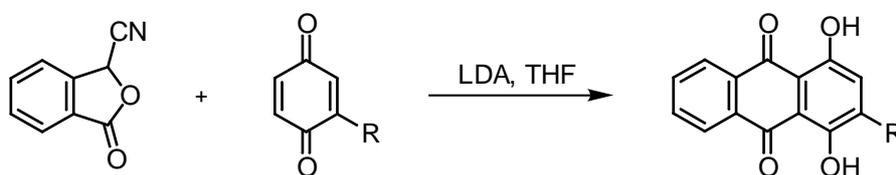
## Exercise 197



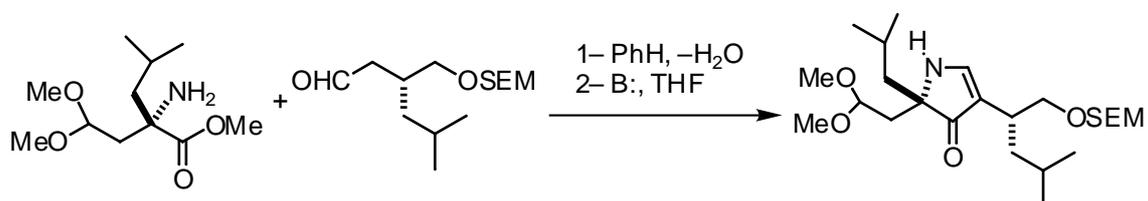
## Exercise 198



## Exercise 199



## Exercise 200



# SOLUTIONS



# Chapter 1

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## Good-Leaving Groups on $sp^3$ Carbons: Substitution and Elimination Reactions of Simple Alkenes

### Exercise 1

1– The alcohol is transformed in a mesylate that is attacked intramolecularly by the nitrogen.

Imamura, H.; Shimizu, A.; Sato, H.; Sugimoto, Y.; Sakuraba, S.; Nakajima, S.; Abe, S.; Miura, K.; Nishimura, I.; andamada, K.; and Morishima, H., *Tetrahedron*, **56**, 7705 (2000).

### Exercise 2

1– Thionyl chloride transforms the alcohol into an alkyl chloride.

2– The amide oxygen displaces intramolecularly the chlorine atom.

Evans, D.A.; Gage, J.R.; and Leighton, J.L., *J.Am.Chem.Soc.*, **114**, 9434 (1992).

### Exercise 3

1– The Lewis acid  $BBr_3$  complexes with the ether oxygen, which becomes a good-leaving group.

2– The complex delivers a bromide anion that attacks the alkene via an  $S_N2$  mechanism. This leads to a double-bond migration and expulsion of the ether oxygen.

Jotterand, N.; and Vogel, P., *J.Org.Chem.*, **64**, 8973 (1999).

### Exercise 4

1– The lithium hexamethyldisilylazide generates an anion on  $\alpha$  to the sulfone.

2– This anion evolves by expulsion of the carbamate nitrogen, causing the formation of an

olefin. The stabilization of the negative charge on the nitrogen by delocalization on the lactone carbonyl makes this expulsion possible.

Leung–Toung, R.; Liu, Y.; Muchowski, J.M.; and Wu, Y.–L., *J.Org.Chem.*, **63**, 3235 (1998).

### Exercise 5

- 1– The *m*-chloroperbenzoic acid epoxidizes one of the alkenes.
- 2– The secondary alcohol attacks the epoxide, producing its opening.

Johnston, J.N.; Tsui, H.–C.; and Paquette, L.A., *J.Org.Chem.*, **63**, 129 (1998).

### Exercise 6

- 1– The hemiacetal hydroxy group is protonated, thus becoming a good-leaving group. An elimination gives rise to one of the double bonds of the final furan.
- 2– The oxygen of the remaining tetrahydrofuran suffers elimination, after protonation, producing the second double-bond in the final furan ring.

Yu, P.; Andang, Y.; Zhang, Z.Y.; Mak, T.C.W.; and Wong, H.N.C., *J.Org.Chem.*, **62**, 6359 (1997).

### Exercise 7

- 1– A bromonium cation on a three-membered ring is formed by attack of the alkene on a bromine molecule.
- 2– One of the alcohols attacks intramolecularly a carbon holding the bromonium cation, producing the opening of the three-membered ring and the breakage of a carbon–bromine bond.

Takahashi, A.; Aso, M.; Tanaka, M.; and Suemune, H., *Tetrahedron* **56**, 1999 (2000).

### Exercise 8

- 1– The oxygen on the ether bridge suffers an elimination after protonation, leading to an alkene conjugated with an ester.
- 2– The resulting alcohol undergoes an elimination after protonation, producing an aromatic pyridine ring.

Ohba, M.; Kubo, H.; and Ishibashi, H., *Tetrahedron* **56**, 7751 (2000).

**Exercise 9**

- 1– After activation by complexation with boron trifluoride, the epoxide suffers and intramolecular attack by an alkene, producing a tertiary carbocation.
- 2– Two possible alkenes are produced by proton loss from the carbocation.

Matsuda, H.; Kageura, T.; Inoue, Y.; Morikawa, T.; and Yoshikawa, M., *Tetrahedron* **56**, 7763 (2000).

**Exercise 10**

- 1– Both the alcohol and the amine are tosylated.
- 2– Under the biphasic basic conditions, an anion formed on the nitrogen of the sulfonamide displaces the tosylate.

Sledeski, A.W.; Kubiak, G.G.; O'Brien, M.K.; Powers, M.R.; Powner, T.H.; and Truesdale, L.K., *J.Org.Chem.*, **65**, 8114 (2000).

**Exercise 11**

The expected reaction would be the formation of a primary alcohol by hydrolysis of the primary bromide. Nevertheless, the hindered neopentyl nature of the bromide causes the unexpected formation of a tertiary alcohol

- 1– One of the carbons of the non-conjugated alkene migrates to the carbon holding the bromine atom, producing the expulsion of bromide and the formation of a tertiary carbocation.
- 2– The tertiary carbocation is trapped by water.

Hua, D.H.; Takasu, K.; Huang, X.; Millward, G.S.; Chen, Y.; and Fan, J., *Tetrahedron*, **56**, 7389 (2000).

**Exercise 12**

- 1– The amine attacks intramolecularly the epoxide, producing its opening and the formation of an alcohol.
- 2– The amine displaces the tosylate.

Pearson, W.H.; and Hines, J.V., *J.Org.Chem.*, **65**, 5785 (2000).

### Exercise 13

- 1– The reaction looks like a simple epoxide opening by attack of hydroxide. In fact, it is more complex. The base generates an alkoxide on the primary alcohol. The alkoxide attacks intramolecularly the epoxide, yielding a secondary alcohol and a new epoxide. This is called a Payne transposition.
- 2– The new epoxide is attacked on its less hindered position by hydroxide.

Suzuki, Y.; Nishimaki, R.; Ishikawa, M.; Murata, T.; Takao, K.; and Tadano, K., *J.Org.Chem.*, **65**, 8595 (2000).

### Exercise 14

A superficial analysis could lead to think that there is a trivial reductive epoxide opening by attack of a hydride ion on one of the carbons of the oxirane. Nevertheless, the appearance of the deuterium on the upper side shows that this is not the case. On the other hand, a direct hydride attack on the oxirane would meet a strong steric hindrance.

The presence of a proximal alcohol allows the operation of the so-called Payne rearrangement, which transforms the initial alcohol in other epoxide. The new epoxide is able to suffer easily the attack of a hydride. The following steps operate:

- 1– A hydride acts as a base, producing the deprotonation of the alcohol.
- 2– The resulting alkoxide attacks the epoxide, yielding a new epoxide, with the oxygen pointing downwards, and a new alkoxide.
- 3– The new epoxide suffers easily the attack of a hydride ion on its less hindered carbon atom. This results in the reductive opening of the epoxide and introduction of a deuterium on the upper face.

Zhu, Jie; Andang, J.-Y.; Klunder, A.; Liu, Z.-Y.; and Zwanenburg, B., *Tetrahedron*, **51**, 5847 (1995).

### Exercise 15

- 1– The alkene attacks the protonated epoxide, producing its opening and the formation of a tertiary carbocation.
- 2– The carbocation is captured by water, leading to the formation of a tertiary alcohol.
- 3– A lactone is formed by condensation between the alcohol liberated on opening the epoxide, and the carboxylic acid.

Paquette, L.A.; Sturino, C.F.; Wang, X.; Prodger, J.C.; and Koh, D. *J.Am.Chem.Soc.*, **118**, 5620 (1996).

**Exercise 16**

- 1– An intramolecular hetero-Diels-Alder reaction in which an alkyne functions as a dienophile, generates a dihydropyridine.
- 2– This dihydropyridine aromatizes by methanol loss.

Boger, D.L.; Ichikawa, S.; and Jiang, H., *J.Am.Chem.Soc.*, **122**, 12169 (2000).

**Exercise 17**

- 1– The alkene attacks the IBr, resulting in the bromide displacement and formation of a iodonium ion inside a three-membered ring.
- 2– The oxygen of the carbonyl in the carbonate attacks intramolecularly one of the carbons in the three-membered ring, resulting in the displacement of the iodonium ion
- 3– A *tert*-butyl cation is lost and trapped by the bromide anion, with the simultaneous formation of the carbonyl double bond in the final cyclic carbonate.

Marshall, J.A.; and Fitzgerald, R.N., *J.Org.Chem.*, **64**, 4477 (1999).

**Exercise 18**

- 1– The furan ring attacks, by its less hindered  $\alpha$  position, the electrophilic bromine atom in the *N*-bromosuccinimide, producing a cation.
- 2– This cation is trapped by the hydroxyde anion present in the basic aqueous solution, resulting in a 2,4-dihydrofuran substituted by a bromine atom and a hydroxy group.
- 3– This intermediate dihydrofuran volves through an electronic movement beginning in the hydroxyl electron-pair, and ending by expulsion of bromide, leading to a furan aromatic ring.

Kobayashi, Y.; and Okui, H., *J.Org.Chem.*, **65**, 612 (2000).

**Exercise 19**

- 1– One of the epoxides is protonated by acetic acid.
- 2– Acetic acid attacks the protonated epoxide, producing its opening, with formation of an acetate and an alcohol.
- 3– The alcohol attacks intramolecularly the neighbouring protonated epoxide, forming the tetrahydrofuran.

Capon, R.J.; and Barrow, R.A., *J.Org.Chem.*, **63**, 75 (1998).

**Exercise 20**

- 1– The alkanesulfonic acid protonates the vinyl ether, giving a carbocation on  $\alpha$  to the oxygen.
- 2– The methylene group bonded to the alcoholic carbon migrates to the carbocation, causing the expansion of the five-membered carbocycle to a six-membered carbocycle, and the formation of a protonated ketone.
- 3– The deprotonation of the ketone yields the final compound.

Paquette, L.A.; and Wang, H.-L., *J.Org.Chem.*, **61**, 5352 (1996).

**Exercise 21**

- 1– The triphenylphosphine reacts with the tetrabromomethane producing a bromophosphonium salt that transforms the alcohol into a bromide.
- 2– The bromine is displaced by attack of the alkene in the silyl enol ether, forming a cyclopropane and a carbocation on  $\alpha$  to the silyl ether oxygen.
- 3– The removal of a proton transforms this carbocation in a silyl ether in which the alkene has migrated.

Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; and Kuwajima, I., *J.Am.Chem.Soc.*, **122**, 3811 (2000).

**Exercise 22**

- 1– A Diels-Alder reaction takes place between the alkene of the vinyl ether and the diazine.
- 2– The resulting intermediate loses nitrogen by means of a retro-hetero-Diels-Alder reaction.
- 3– The resulting dihydrobenzene aromatizes by losing methanol.

Boger, D.L.; and Wolkenberg, S.E., *J.Org.Chem.*, **65**, 9120 (2000).

**Exercise 23**

- 1– The sodium azide works as a base taking a proton from the alcohol.
- 2– The resulting alkoxide displaces intramolecularly one of the chlorine atoms, giving an epoxide.
- 3– An azide anion attacks the epoxide on its more substituted carbon, producing its opening, with formation of an  $\alpha$ -chloroalkoxide.
- 4– The  $\alpha$ -chloroalkoxide evolves with expulsion of a chloride anion and formation of an aldehyde.

The crown ether is added to increase the nucleophilicity of the azide anion.

Yoshikawa, M.; Andokokawa, Y.; Okuno, Y.; and Murakami, N., *Tetrahedron*, **51**, 6209 (1995).

### Exercise 24

1– The oxygen of one of the epoxides displaces intramolecularly the proximal mesylate, producing an intermediate with an oxygen atom bearing a positive charge and taking part of two three-membered rings.

2– The oxygen of the other epoxide displaces the positively charged oxygen, opening one of the three-membered rings and generating a new positively charged oxygen. This positively charged oxygen is shared by a three-membered and a five-membered ring.

3– One of the oxygens of the mesylate displaces the positively charged oxygen, giving an epoxide where the oxygen is positively charged and bears a mesyl group.

4– The methoxide, generated in the reaction media, attacks the mesyl group, producing the liberation of the epoxide and the formation of methyl mesylate.

Observe that the intermediate oxonium salts are stabilized by the high polarity of the methanol used as a solvent.

Morimoto, Y.; Iwai, T.; and Kinoshita, T., *J.Am.Chem.Soc.*, **121**, 6792 (1999).



## Chapter 2

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### Additions to Aldehydes and Ketones

#### Exercise 25

1– The catalytic hydrogenation causes the debenylation of an amine that attacks the aldehyde producing a stable aminal.

Yu, P.; Wang, T.; and Cook, J.M., *J.Org.Chem.*, **65**, 3173 (2000).

#### Exercise 26

1– Acidic methanolysis of the acetal leads to the formation of a diol and 2-methylcyclohexanone dimethyl acetal.

2– An intramolecular condensation between the diol and the furyl ketone leads to the cyclic acetal.

Sugimura, T.; Tai, Akira; and Koguro, K., *Tetrahedron*, **50**, 11647 (1994).

#### Exercise 27

1– Both isopropylidene acetals suffer an acidic methanolysis, producing the liberation of four alcoholic functions.

2– Two of the freed alcohols form a cyclic acetal by condensation with the ketone.

Dondoni, A.; Marra, A.; and Merino, P., *J.Am.Chem.Soc.*, **116**, 3324 (1994).

#### Exercise 28

1– The hydrofluoric acid produces the hydrolyses of the triethylsilyl ethers.

2– Two of the free alcohols react with the ketone, forming a cyclic acetal.

Evans, D.A.; Gage, J.R.; and Leighton, J.L., *J.Am.Chem.Soc.*, **114**, 9434 (1992).

### Exercise 29

There is a double reductive amination where diphenylmethylamine reacts with the ketone and with the aldehyde, which is in equilibrium with the hemiacetal.

Dhavale, D.D.; Saha, N.N.; and Desai, V.N., *J.Org.Chem.*, **62**, 7482 (1997).

### Exercise 30

This is an example of a Paal-Knorr synthesis of pyrrole. It consists in a double condensation of a primary amine with a 1,4-diketone, giving a cyclic bis-enamine, which happens to be an aromatic pyrrole ring. The Ti(IV) tetra-isopropoxide acts as a Lewis acid in catalytic quantities

Dong, Y.; Pai, N.N.; Ablaza, S.L.; Andu, S.–X.; Bolvig, S.; Forsyth, D.A.; and Le Quesne, P.W., *J.Org.Chem.*, **64**, 2657 (1999).

### Exercise 31

1– The tetra-*n*-butylammonium fluoride (TBAF) produces the desilylation of the silyl ether, leading to an alkoxide.

2– The alkoxide evolves by ketone formation and migration of an oxygen atom to a neighbouring carbon, producing the expulsion of the mesylate.

As an alternative mechanism, the alkoxide may form the ketone by expulsion of oxygen. This generates another alkoxide that displaces intramolecularly the mesylate.

Ishihara, J.; Nonaka, R.; Terasawam Y.; Shiraki, R.; Andabu, K.; Kataoka, H.; Ochiai, Y.; and Tadano, K., *J.Org.Chem.*, **63**, 2679 (1998).

### Exercise 32

1– The acidic conditions, generated by pyridinium *p*-toluenesulfonate in ethanol, produces the dioxolane ethanolysis.

2– The protonation of one of the diethyl acetal oxygen atoms is followed by the loss of ethanol, resulting in the formation of a cation on  $\alpha$  to one oxygen. This cation is attacked by one of the alcohols.

Paquette, L.A.; Zeng, Q.; Tsui, H.-C.; and Johnson, J.N., *J.Org.Chem.*, **63**, 8491 (1998).

### Exercise 33

- 1– The perchloric acid produces the hydrolysis of the acetal.
- 2– The amine attacks the liberated ketone, giving the final cyclic imine.

Wu, B.; and Bai, D., *J.Org.Chem.*, **62**, 5978 (1997).

### Exercise 34

- 1– The chlorine is displaced by a hydroxide giving a cyanohydrin.
- 2– The cyanohydrin is transformed in a ketone under basic conditions.

Marshall, K.A.; Mapp, A.K.; and Heathcock, C.H., *J.Org.Chem.*, **61**, 9135 (1996).

### Exercise 35

- 1– A Boc-protected amine and an alcohol are liberated by acidic hydrolysis of the oxazolidine.
- 2– One of the nitrogen atoms attacks intramolecularly the aldehyde producing a stable cyclic aminal.

Soro, P.; Rassa, G.; Spanu, P.; Pinna, L.; Zanardi, F.; and Casiraghi, G., *J.Org.Chem.*, **61**, 5172 (1996).

### Exercise 36

- 1– The acidic conditions produce the release, after protonation, of a methoxy group from the anomeric position.
- 2– The resulting cation is attacked intramolecularly by the oxygen of the phenol.

Hauser, F.M.; and Ganguly, D., *J.Org.Chem.* **65**, 1842 (2000).

**Exercise 37**

- 1– The Wittig ylide reacts with the aldehyde, in equilibrium with a hemiacetal, yielding an alkene.
- 2– The liberated alcohol, which exists as an alkoxide under the basic reaction conditions, displaces intramolecularly the iodide, producing a tetrahydrofuran.

Ruan, Z.; Dabideen, D.; Blumenstein, M.; and Mootoo, D.R., *Tetrahedron* **56**, 9203 (2000).

**Exercise 38**

- 1– The methanol attacks the ketone, producing a hemiacetal.
- 2– The protonation of the alkene yields a carbocation located on  $\alpha$  to the tetrahydrofuran oxygen. The hemiacetal hydroxy group reacts intramolecularly with this cation.

Crimmins, M.T.; Pace, J.M.; Nantermet, P.G.; Kim-Meade, A.S.; Thomas, J.B.; Watterson, S.H.; and Wagman, A.S., *J.Am.Chem.Soc.* **122**, 8453 (2000).

**Exercise 39**

- 1– The base generates an enolate on the ester, and it reacts with the imine.
- 2– The resulting nitrogen anion displaces intramolecularly the chloride, yielding an aziridine.

Vedejs, E.; Piotrowski, D.W.; and Tucci, *J.Org.Chem.*, **65**, 5498 (2000).

**Exercise 40**

- 1– The Boc group is removed under acidic conditions.
- 2– The resulting amine condensates intramolecularly with the aldehyde.

Stark, L.M.; Lin, X.; and Flippin, L.A., *J.Org.Chem.*, **65**, 3227 (2000).

**Exercise 41**

The acidic conditions lead to the opening of the epoxide with formation of a diol that reacts with acetaldehyde, producing one of the products.

Alternatively, the diol hydroxy group forming part of a hemiacetal may generate an aldehyde, and the two remaining hydroxy groups may form an acetal by reaction with acetaldehyde.

Bélanger, G.; and Deslongchamps, P., *J.Org.Chem.*, **65**, 7070 (2000).

### Exercise 42

- 1– Acetal hydrolysis yields a diol.
- 2– One of the alcohols produces a hemiacetal by attack on the ketone.
- 3– Both alcohols suffer an acid-catalysed dehydration, leading to an aromatic furan ring.

Oka, T.; and Murai, A., *Tetrahedron*, **54**, 1 (1998).

### Exercise 43

- 1– The acetal is hydrolysed, resulting in the formation of an aldehyde and the deprotection of a diol.
- 2– The liberated secondary hydroxyl attacks the aldehyde, forming a hemiacetal.

Alternatively, a simpler mechanism, with no need to liberate the aldehyde, can be proposed. It consists in:

- 1– Protonation of one of the acetal oxygen atoms, followed by expulsion of oxygen and formation of a carbocation in the  $\alpha$  position of the oxygen of a pyranose ring.
- 2– Trapping of the carbocation by water.

Barbaud, C.; Bols, M.; Lundt, I.; and Sierks, M., *Tetrahedron*, **51**, 9063 (1995).

### Exercise 44

- 1– The acidic conditions cause the acetal hydrolysis and the removal of the Boc group.
- 2– The distal alcohol reacts with the aldehyde producing a hemiacetal.
- 3– The hemiacetal is transformed in a methyl glycoside, under the action of acidic methanol.

Jurczak, J.; Kozak, J.; and Golebiowski, A., *Tetrahedron*, **48**, 4231 (1992).

### Exercise 45

- 1– The acidic media leads to the hydrolysis of the ethylene acetal.

- 2– The resulting ketone, after being activated by protonation, is attacked intramolecularly by the aromatic ring. This leads to a Wheland intermediate that loses a proton.
- 3– An enone is formed by dehydration of the alcohol, previously activated by protonation.

Nicolau, K.C.; and Dai, W.-M., *J.Am.Chem.Soc.*, **114**, 8908 (1992).

### Exercise 46

- 1– The thiourea sulfur atom displaces the bromine positioned  $\alpha$  to a ketone, producing a sulfonium salt.
- 2– Both carbon-nitrogen double bonds migrate so as to generate an aromatic isotiazole ring

Beaulieu, P.L.; Gillard, J.; Bailey, M.; Beaulieu, C.; Duceppe, J.-S.; Lavallée, P.; and Wernic, D., *J.Org.Chem.*, **64**, 6622 (1999).

### Exercise 47

- 1– The trifluoroacetic acid produces the removal of the Boc group.
- 2– The acidic media produces the epimerization of the position  $\alpha$  to the ketone. This allows the formation of an epimer able to cyclize with the amine.
- 3– The resulting amine reacts intramolecularly with the ketone, yielding a cyclic imine.

Collado, I.; Ezquerra, J.; Mateo, A.I.; Pedregal, C.; and Rubio, A., *J.Org.Chem.*, **64**, 4304 (1999).

### Exercise 48

- 1– An aldehyde is formed by hydrolysis of the acetal.
- 2– The aldehyde reacts intramolecularly with the amine, producing an iminium salt.
- 3– The enol form of the ketone reacts with the iminium salt.

Scott, R.W.; Epperson, J.; and Heathcock, C.H., *J.Org.Chem.*, **63**, 5001 (1998).

### Exercise 49

- 1– An ozonolysis leads to the alkene breakage, with the formation of a dialdehyde.
- 2– One of the aldehydes tautomerizes to an enol.

3– Acetic acid catalyses the formation of a cyclic acetal by reaction of the remaining aldehyde with the enol and the hemiacetal hydroxy groups.

Chang, M.–Y.; Chang, C.–P.; Andin, W.–K.; and Chang, N.–C., *J.Org.Chem.*, **62**, 641 (1997).

### Exercise 50

1– The ammonia, liberated from the ammonium acetate, condenses with the aldehyde, producing an imine.

2– The sodium cyanoborohydride reduces the imine to a primary amine.

3– The primary amine produces a first cycle by an intramolecular reaction with the epoxide, and a second cycle by displacement of bromide.

Hunt, J.A.; and Roush, W.R., *J.Org.Chem.*, **62**, 1112 (1997).

### Exercise 51

1– The alcohol reacts intramolecularly with one of the ketones, giving a hemiacetal.

2– The hydroxy group from the acetal is protonated under acidic conditions, giving an alkyloxonium compound that loses water, and evolves to a carbocation which is stabilized by extensive conjugation.

3– One of the resonant forms of this carbocation with extended conjugation is an enone protonated on the oxygen. The deprotonation of this enone leads to the final compound.

Danheiser, R.L.; Casebier, D.S.; and Firooznia, F., *J.Org.Chem.*, **60**, 8341 (1995).

### Exercise 52

1– There is a standard ozonolysis by ozone treatment followed by reduction of the ozonide, producing an aldehyde and a ketone.

2– The alcohol reacts intramolecularly with the ketone, giving a hemiacetal

3– The hydroxy group from the hemiacetal attacks the aldehyde, yielding a new hemiacetal

Takao, K.; Ochiai, H.; andoshida, K.; Hashizuka, T.; Koshimura, H.; Tadano, K.; and Ogawa, S., *J.Org.Chem.*, **60**, 8179 (1995).

**Exercise 53**

- 1– Deprotection of the trityl and the isopropylidene groups under acidic conditions leads to the formation of two alcohols and a hemiacetal, which equilibrates with a hydroxy aldehyde.
- 2– The alcohol on position 2 displaces intramolecularly one of the mesylates, leading to a tetrahydrofuran.
- 3– The ethylene glycol reacts with the aldehyde, under acidic catalysis, producing a dioxolane.

Popsavin, V.; Beric, O, Popsavin, M., Radic, L.; Csanádi, J.; and Cirin-Novta, V., *Tetrahedron* **56**, 5929 (2000).

**Exercise 54**

- 1– The nitrogen, protected with Boc, reacts intramolecularly with the ketone, giving a aminal that dehydrates to an indole.
- 2– The amide nitrogen attacks the aldehyde, generating an aminal which losses a hydroxide after oxygen protonation, generating an acyliminium cation.
- 3– The position 3 of the indole reacts with the acyliminium cation.

Toczko, M.A.; and Heathcock, C.H., *J.Org.Chem.*, **65**, 2642 (2000).

**Exercise 55**

- 1– The Cbz and the Bn protecting groups are removed under catalytic hydrogenation.
- 2– The liberated amine reacts intramolecularly with the aldehyde in equilibrium with an hemiacetal, generating an imine.
- 3– The imine is reduced to an amine by catalytic hydrogenation.

Saha, N.N.; Desai, V.N.; and Dhavale, D.D., *Tetrahedron*, **57**, 39 (2001).

**Exercise 56**

The starting molecule contains three acetal functional groups. One is a MOM protecting group, another one is a spiro acetal joining two six-membered cycles, and the third one is a spiro acetal connecting a six-membered ring to a three-membered one. This last acetal is very reactive, because it contains oxygen inside a three-membered ring with great tension.

- 1– The PPTS acts as a mild acid, which protonates the oxygen in the three-membered ring. This protonated oxygen becomes a very good leaving-group, because of its positive charge, and because its departure allows the release of the tension in the three-membered ring.

2– An electronic movement begins with the breakage of one of the C–O bonds of the spiro acetal connecting the two six-membered rings. It continues with formation of a carbon-oxygen double bond—that is, the aldehyde—and finishes with the expulsion of the protonated oxygen on the three-membered cycle. This generates a carbocation on  $\alpha$  to oxygen.

3– This carbocation is attacked by the hydroxyl group liberated during the opening of the three-membered cycle.

Ireland, R.E.; Armstrong, J.D.; Lebreton, J.; Meissner, R.S.; and Rizzacasa, M.A., *J.Am.Chem.Soc.*, **115**, 7152 (1993).

### Exercise 57

1– The hydroxylamine nitrogen attacks one of the aldehydes, giving a  $\alpha$ -aminoalcohol.

2– An attack to the other aldehyde allows the formation of a bis- $\alpha$ -aminoalcohol, where both  $\alpha$ -amino alcohols share the same nitrogen atom.

3– Both bis- $\alpha$ -amino alcohol hydroxyls suffer a dehydration, producing a bis-enamine, where both enamines share the same nitrogen atom. This bis-enamine can be described as a *N*-hydroxydihydropyridine.

4– The *N*-hydroxydihydropyridine loses water, resulting in aromatization to the final pyridine.

Li, J.; Wang, T.; Andu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D.; and Cook, J.M., *J.Am.Chem.Soc.*, **121**, 6998 (1999).

### Exercise 58

1– The *ipso* position of the carbon substituent in the furan ring attacks the bromine in the *N*-bromosuccinimide.

2– The resulting cation is attacked by water on the furan  $\alpha$  position, which is not bearing a carbon radical. This results in the formation of a hemiacetal.

3– An electronic movement, beginning with the electron pair on the hemiacetal hydroxy group, produces the rupture of the oxygenated ring, and results in the formation of an aldehyde and a ketone, and expulsion of a bromide anion.

4– The alcohol reacts with the aldehyde, giving the final hemiacetal.

Arai, Y.; Masuda, T.; Andoneda, S.; Masaki, Y.; and Shiro, M., *J.Org.Chem.*, **65**, 258 (2000).

### Exercise 59

1– One of the acetal oxygen atoms attacks the protonated epoxide, producing its opening.

- 2– A heterolytic cleavage of the acetal ring yields a carbocation on  $\alpha$  to an oxygen.
- 3– A new acetal is formed by methoxy transfer from 2,2-dimethoxypropane to the carbocation. The acidic conditions produce the acetal opening with liberation of an alcohol and protonated acetone.
- 4– The resulting vicinal diol is ketalized with 2,2-dimethoxypropane under acidic conditions.

Yu, Q.; Andao, Z.-J.; Chen, X.-G.; and Wu, Y.-L., *J.Org.Chem.*, **64**, 2440 (1999).

### Exercise 60

- 1– A methanolysis under acidic conditions produces the removal of the diethyl acetal and MEM protecting groups.
- 2– The liberated alcohol reacts intramolecularly with the aldehyde, generating a hemiacetal.
- 3– The hydroxyl of the hemiacetal is lost after protonation, leading to a carbocation on  $\alpha$  to an oxygen.
- 4– This cation is trapped by methanol.

Hauser, F.M.; and Ganguly, D., *J.Org.Chem.* **65**, 1842 (2000).

### Exercise 61

- 1– The chlorine atom is displaced by the nitrogen of a formamide molecule.
- 2– Another formamide molecule reacts with the ketone yielding an *N*-formylenamide.
- 3– A nitrogen atom attacks intramolecularly the carbonyl of one of the formyl groups, producing an *N*-formylimidazole after water loss.
- 4– The attack of a water molecule produces the removal of a formyl group.

Hayashi, Y.; Orikasa, S.; Tanaka, K.; Kanoh, K.; and Kiso, Y., *J.Org.Chem.*, **65**, 8402 (2000).

### Exercise 62

- 1– Condensation of hydroxylamine with one of the ketones results in the formation of an oxime.
- 2– The oxime tautomerizes to a *N*-hydroxyenamine.
- 3– The nitrogen attacks the remaining ketone yielding a *N*-hydroxydienamine.
- 4– Aromatization to a pyridine ring occurs by loss of a water molecule.

Hagiwara, H.; Katsumi, T.; Kamat, V.P.; Hoshi, T.; Suzuki, T.; and Ando, M., *J.Org.Chem.*, **65**, 7231 (2000).

**Exercise 63**

- 1– The acidic methanolysis of the isopropylidene acetal liberates a diol, and generates 2,2-dimethoxypropane.
- 2– The resulting secondary alcohol attacks the ketone, giving a six-membered cyclic hemiacetal. No attack from the primary alcohol occurs because it would generate a less favourable seven-membered cyclic hemiacetal.
- 3– The hemiacetal hydroxy group is protonated.
- 4– The protonated hydroxy group is lost as water. This results in the formation of an oxygen-stabilized carbocation.
- 5– The carbocation is attacked by a methanol molecule.

Dondoni, A.; Marra, A.; and Merino, P., *J.Am.Chem.Soc.*, **116**, 3324 (1994).

**Exercise 64**

- 1– The MnO<sub>2</sub> oxidises the allylic alcohol to an aldehyde.
- 2– The hydrochloric acid hydrolyses the tetrahydropyranyl ether.
- 3– The liberated alcohol attacks the aldehyde, producing a hemiacetal.
- 4– The hemiacetal hydroxy group is protonated, becoming a good-leaving group which is expelled, generating an oxygen-stabilized allylic cation.
- 5– A deprotonation leads to an aromatic furan ring.

Fürstner, A.; Guth, O.; Rumbo, A.; and Seidel, G., *J.Am.Chem.Soc.*, **121**, 11108 (1999).

**Exercise 65**

- 1– The catalytic hydrogenation leads to the removal of the Cbz protecting group.
- 2– The amine attacks the aldehyde, which is in equilibrium with a hemiacetal, giving an  $\alpha$ -aminoalcohol.
- 3– The  $\alpha$ -aminoalcohol suffer a dehydration to an imine.
- 4– The imine is reduced by catalytic hydrogenation.

Tschamber, T.; Backenstrass, F.; Neuburger, M.; Zehnder, M.; and Streith, J., *Tetrahedron*, **50**, 1135 (1994).

**Exercise 66**

- 1– The catalytic hydrogenation produces the removal of the Cbz protecting group.
- 2– The resulting  $\alpha$ -aminoalcohol is dehydrated to an imine.

- 3– An amine is formed by catalytic hydrogenation of the imine.
- 4– This amine is reductively alkylated by *n*-propenal under catalytic hydrogenation.

Tschamber, T.; Backenstrass, F.; Neuburger, M.; Zehnder, M.; and Streith, J., *Tetrahedron*, **50**, 1135 (1994).

## Chapter 3

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### Derivatives of Carboxylic Acids

#### Exercise 67

- 1– The anhydride in the starting compound suffers a basic hydrolysis, producing a  $\beta$ -keto acid.
- 2– The  $\beta$ -keto acid is decarboxylated on heating.

Goverdhan, M.; Shailesh, R.; and Venkateswarlu, Y., *Tetrahedron*, **50**, 11729 (1994).

#### Exercise 68

- 1– Both acetals suffer an acidic hydrolysis.
- 2– One of the liberated alcohols attacks the protonated carbonyl of the methyl ester, producing the elimination of methanol and formation of a  $\delta$ -lactone.

Yoshikawa, M.; Andokokawa, Y.; Okuno, Y.; and Murakami, N., *Tetrahedron*, **51**, 6209 (1995).

#### Exercise 69

- 1– The catalytic hydrogenation produces the reductive breakage of the N–O bond, liberating an amine and an alcohol.
- 2– The amine attacks one of the esters, displacing, via an addition-elimination mechanism, an ethoxide, and generating a lactam.

Snider, B.B.; and Lin, H., *J.Am.Chem.Soc.*, **121**, 7778 (1999).

#### Exercise 70

- 1– The methyllithium attacks the lactam carbonyl and causes the expulsion of an amide.

- 2– The resulting amide produces the opening of the epoxide by an intramolecular attack.

Parsons, P.J.; Camp, N.P.; Edwards, N.; and Sumoreeah, L.R., *Tetrahedron*, **56**, 309 (2000).

### Exercise 71

- 1– The sulfur atom attacks the cyanide, generating a carbon-nitrogen double-bond.
- 2– The amine attacks the carbon-nitrogen double-bond, producing an intermediate that loses ammonia.

Zamri, A.; and Abdallah, M.A., *Tetrahedron*, **56**, 249 (2000).

### Exercise 72

- 1– The strong base DBU captures the alcohol proton.
- 2– The resulting alkoxide attacks the lactone carbonyl and expels an oxygen.

Chen, M.-J.; Narkunan, K.; and Liu, R.-S., *J.Org.Chem.*, **64**, 8311 (1999).

### Exercise 73

- 1– The pyridinium *p*-toluenesulfonate (PPTS) generates a mild acidic medium that allows the selective hydrolysis of the oxazoline. This happens by protonation of the nitrogen, followed by an electronic movement that begins in the electron pair in one of the oxygen atoms in the bridge-head acetal, and produces the expulsion of the oxazoline oxygen.
- 2– This generates a cation on  $\alpha$  to the oxygen, which is trapped by water.

Williams, D.R.; Rojas, C.M.; and Bogen, S.L., *J.Org.Chem.*, **64**, 736 (1999).

### Exercise 74

In this reaction, an apparently simple alcohol acetylation fails because of a very easy elimination that leads to aromatization.

- 1– The alcohol is acetylated by the normal acetylation mechanism of alcohols, in which acid chlorides and pyridine are used.

2– This is followed by a 1,4-elimination, where pyridine acts as base and an acetate as leaving group. This elimination is particularly easy because it leads to an aromatic ring.

Chiacchio, U; Rescifina, A.; Iannazzo, D.; and Romeo, G., *J.Org.Chem.*, **64**, 28 (1999).

### Exercise 75

1– Ammonia, which is present in a small proportion in equilibrium with the ammonium cation, attacks one of the ketones, producing an enamine.

2– The nitrogen of the resulting enamine condenses intramolecularly with the carboxylic acid, giving a lactam.

Guarna, A.; Occhiato, E.G.; Machetti, F.; and Scarpi, D., *J.Org.Chem.*, **63**, 4111 (1998).

### Exercise 76

1– The amine is alkylated by phenyl bromoacetate.

2– Deprotonation of the secondary alcohol is followed by attack of the resulting alkoxide on the phenyl ester.

Angle, S.R.; and Henry, R.M., *J.Org.Chem.*, **63**, 7490 (1998).

### Exercise 77

1– The methoxide, generated by the action of the potassium carbonate on methanol, reacts with the lactone. This produces a methyl ester and an alkoxide.

2– The resulting alkoxide reacts intramolecularly with the iodide, forming an epoxide.

Ziegler, F.E.; and Wang, Y., *J.Org.Chem.*, **63**, 7920 (1998).

### Exercise 78

1– The Dibal-H, at a low temperature, reduces the lactone to the corresponding hemiacetal.

2– This hemiacetal equilibrates with a hydroxy aldehyde, whose aldehyde group is attacked by the alcohol in position 5.

Sibi, M.P.; Lu, J.; and Edwards, J., *J.Org.Chem.*, **62**, 5864 (1997).

**Exercise 79**

- 1– The phosphonate  $\alpha$ -anion reacts with the lactone carbonyl. This produces the opening of the lactone and the formation of a  $\beta$ -keto phosphonate and an enol, which tautomerizes to a ketone.
- 2– An anion on the  $\beta$ -keto phosphonate is formed, thanks to the use of excess of basic phosphorous reagent. This anion reacts intramolecularly with the ketone.

Grzywacz, P.; Marczak, S.; and Wicha, J., *J.Org.Chem.*, **62**, 5293 (1997).

**Exercise 80**

The acidic conditions produce the deprotection of the tetrahydropyranyl ether, the dehydration of the alcohol, and the formation of the lactone.

Andrus, M.B.; Li, W.; and Keyes, R.F., *J.Org.Chem.*, **62**, 5542 (1997).

**Exercise 81**

- 1– Methoxide attack on the lactone carbonyl produces the opening of the lactone, and the formation of a methyl ester.
- 2– The basic conditions produce the migration of the alkene into conjugation with the ester carbonyl.

Posner, G.H.; Lee, J.K.; White, M.C.; Hutchings, R.H.; Dai, H.; Kachinski, J.L.; Dolan, P.; and Kensler, T.W., *J.Org.Chem.*, **62**, 3299 (1997).

**Exercise 82**

In this reaction, Jones reagent, which consists in a solution of chromium trioxide in sulfuric acid and acetone, plays a double role as oxidant and as provider of acidic conditions.

- 1– The acidic medium produces the acetal hydrolysis, causing the liberation of an aldehyde.
- 2– The aldehyde is oxidized to an acid, which undergoes lactonization to the final compound.

Fujita, T.; Tanaka, M.; Norimine, Y.; and Suemune, H., *J.Org.Chem.*, **62**, 3824 (1997).

**Exercise 83**

- 1– The acidic conditions produce the hydrolysis of both the amide and the lactone.

2– The carboxylic acid, resulting from the amide hydrolysis, forms a seven-membered lactone with the alcohol liberated from the lactone hydrolysis.

Schultz, A.G.; Malachowski, W.P.; and Pan, Y., *J.Org.Chem.*, **62**, 1223 (1997).

#### Exercise 84

- 1– The acetal suffers an acidic hydrolysis.
- 2– One of the alcohols reacts intramolecularly with the methyl ester, yielding a lactone.

Maezaki, N.; Gijsen, H.J.M.; Sun, L.-Q.; and Paquette, L. *J.Org.Chem.*, **61**, 6685 (1996).

#### Exercise 85

- 1– Sodium hydride reacts with the alcohol, producing an alkoxide and gaseous hydrogen.
- 2– The alkoxide attacks the lactone carbonyl.

Moritani, Y.; Fukushima, C.; Ukita, T.; Miyagishima, T.; Ohmizu, H.; and Iwasaki, T. *J.Org.Chem.*, **61**, 6922 (1996).

#### Exercise 86

- 1– The methoxide attacks the lactone carbonyl producing the formation of a methyl ester and an alkoxide.
- 2– The alkoxide attacks intramolecularly the epoxide, leading to the formation of a tetrahydrofuran and a tertiary alcohol.

Rodríguez, A.D.; Piña, I.C.; Acosta, A.L.; Ramírez, C.; and Soto, J.J., *J.Org.Chem.*, **66**, 648 (2001).

#### Exercise 87

- 1– Activation of the  $\beta$ -lactam by protonation on the carbonyl, allows an intramolecular attack by the secondary alcohol.
- 2– The resulting tetrahedral intermediate evolves by expulsion of a nitrogen atom and formation of a  $\gamma$ -lactone. Observe that, quite exceptionally, a nitrogen atom functions as a good-leaving group instead of an oxygen atom. This happens thanks to the ring strain released during the opening of the  $\beta$ -lactam.

Bose, A.K.; Banik, B.K.; Mathur, C.; Wagle, D.R.; and Manhas, M.S., *Tetrahedron* **56**, 5603 (2000).

**Exercise 88**

- 1– The phenylmagnesium bromide attacks the aldehyde, yielding a magnesium alkoxide. The lactone carbonyl is not attacked due to its lesser reactivity.
- 2– The alkoxide attacks intramolecularly the lactone carbonyl producing a new lactone and liberating an alcohol.

Zhao, Y.; Ku, Y.; Hao, X.J.; and Lee, S., *Tetrahedron* **56**, 8901 (2000).

**Exercise 89**

- 1– The diol reacts intramolecularly under acidic catalysis with the carbonyl of the acetate, producing an ortho ester. This reaction is akin to the formation of acetals by reaction of alcohols with ketones.

Due to the lesser reactivity of ester carbonyl groups relative to ketone carbonyl groups, the reaction described in this problem is quite exceptional, and may happen thanks to very strong proximity effects.

de la Torre, M.C.; Maggio, A.; and Rodríguez, B., *Tetrahedron* **56**, 8007 (2000).

**Exercise 90**

- 1– The attack of methoxide on the acetates produces the liberation of two alkoxides.
- 2– The primary alkoxide can attack intramolecularly the lactone carbonyl, leading to a new lactone, that besides suffers an attack by methoxide on the epoxide. Alternatively, the primary alkoxide can open intramolecularly the epoxide producing an oxetane.

de la Torre, M.C.; Maggio, A.; and Rodríguez, B., *Tetrahedron* **56**, 8007 (2000).

**Exercise 91**

- 1– The methoxide attacks the carbonyl group from the cyclic urethane, and the nitrogen is expelled as a sulfamide anion.
- 2– The anion on the sulfamide nitrogen displaces the iodide, producing an *N*-tosylaziridine.

Fellows, I.M.; Kaelin Jr., D.E.; and Martin, S.F., *J.Am.Chem.Soc.* **122**, 10781 (2000).

**Exercise 92**

The ester carbonyl displaces intramolecularly the mesylate, yielding a carbocation that is trapped by ethanol.

Crimmins, M.T.; Pace, J.M.; Nantermet, P.G.; Kim-Meade, A.S.; Thomas, J.B.; Watterson, S.H.; and Wagman, A.S., *J.Am.Chem.Soc.* **122**, 8453 (2000).

**Exercise 93**

- 1– The acetonide is hydrolysed under acidic conditions.
- 2– The following steps are very similar to the formation of a cyclic acetal by the intramolecular reaction of two alcohols with a ketone. One of the alcohols attacks the ketone, which is previously activated by protonation. This produces a hemiacetal, which is converted to a carbocation by protonation of the hydroxy group and water loss. Finally, the carbocation is trapped intramolecularly by the amide nitrogen.

Nicolau, K.C.; Murphy, F.; Barluenga, S.; Ohshima, T.; Wei, H.; Xu, J.; Gray, D.L.F.; and Baudoin, O., *J.Am.Chem.Soc.*, **122**, 3830 (2000).

**Exercise 94**

- 1– The methoxide, generated by the action of potassium carbonate on methanol, attacks the lactone carbonyl, yielding a methyl ester and an alkoxide.
- 2– The alkoxide displaces intramolecularly the mesylate.

Avedissian, H.; Sinha, S.C.; Andazbak, A.; Sinha, A.; Neogi, P.; Sinha, S.C.; and Keinan, E., *J.Org.Chem.*, **65**, 6035 (2000).

**Exercise 95**

- 1– A hemiacetal is formed by attack of the carboxylic acid on the ketone.
- 2– The hydroxy group on the hemiacetal is acetylated.
- 3– The acetate suffers an acid-catalyzed elimination.

Goverdhan, M.; Shailesh, R.; and Venkateswarlu, Y., *Tetrahedron*, **50**, 11729 (1994).

**Exercise 96**

- 1– The water, aided by the acidic resin, produces the acidic hydrolysis of the isopropylidene acetal.
- 2– The opened form of the hemiacetal is a  $\beta$ -keto acid, which suffers decarboxylation on heating in acetic acid.
- 3– The resulting hydroxy ketone equilibrates with the final hemiacetal, which predominates in the mixture.

Mack, H.; and Brossmer, R., *Tetrahedron*, **54**, 4521 (1998).

**Exercise 97**

- 1– Sodium hydride produces the formation of an anion on the carbamate nitrogen.
- 2– This anion produces the epoxide opening through an intermolecular attack, yielding an alkoxide.
- 3– The alkoxide attacks the carbamate carbonyl, producing the expulsion of an alkoxide.

Tanner, D.; Almario, A.; and Högberg, T., *Tetrahedron*, **51**, 6061 (1995).

**Exercise 98**

- 1– The ammonia, in equilibrium with the ammonium cation, attacks the ketone, producing an enamine.
- 2– The enamine nitrogen attacks the ester carbonyl.
- 3– An aromatic oxazole is formed by water elimination.

Smith III, A.; Friestad, G.K.; Barbosa, J.; Bertounesque, E.; Duan, J.J.-W.; Hull, K.G.; Iwashima, M.; Qiu, Y.; Spoons, P.G.; and Salvatore, B.A., *J.Am.Chem.Soc.*, **121**, 10478 (1999).

**Exercise 99**

- 1– The starting hemiacetal equilibrates with a hydroxy ketone.
- 2– This hydroxy ketone may revert to the starting hemiacetal by intramolecular attack on the carbonyl by one of the hydroxy groups, or evolve to a different hemiacetal by attack of the other hydroxy group.

3– One of the free hemiacetal hydroxy groups with dihydrofuran structure is acetylated. The hydroxy group from the alternative hemiacetal is not acetylated because of the increased steric hindrance derived from the fact that it is a tertiary one.

Chen, X-T.; Bhattacharya, S.K.; Zhou, B.; Gutteridge, C.E.; Pettus, T.R.R.; and Danishefsky, S.J., *J.Am.Chem.Soc.*, **121**, 6563 (1999).

### Exercise 100

- 1– The methoxide anion attacks the lactone carbonyl, resulting in the formation of a methyl ester and an enol.
- 2– The enol tautomerizes to an aldehyde.
- 3– The alkene migrates into conjugation with the aldehyde, by a deprotonation-protonation mechanism.

Fürstner, A.; and Krause, H., *J.Org.Chem.*, **64**, 8281 (1999).

### Exercise 101

- 1– The acidic conditions produce the hydrolysis of the trityl (triphenylmethyl) ether. Normally, the acidic hydrolysis of ethers is very difficult. In this case, the hydrolysis can be done under very mild conditions, due to the stability of the intermediate trityl cation.
- 2– An acidic hydrolysis of the lactone is produced.
- 3– A new five-membered lactone is formed.

Ge. P.; and Kirk, K.L. *J.Org.Chem.*, **61**, 8671 (1996).

### Exercise 102

- 1– The base LHMDS forms an  $\alpha$ -anion on the acetate carbonyl.
- 2– This anion attacks intramolecularly the methyl ester, producing the expulsion of methoxide and the formation of a ketone.
- 3– The resulting ketone tautomerizes to an enol. In this case, the enol form predominates in the equilibrium, because of conjugation between the alkene and the lactone carbonyl.

Ge. P.; and Kirk, K.L. *J.Org.Chem.*, **61**, 8671 (1996).

**Exercise 103**

- 1– The LHMDS deprotonates the alcohol.
- 2– The resulting alcohol reacts with the acetate carbonyl, producing a trans-acetylation.
- 3– This generates the starting compound from the previous exercise, which evolves in a similar way in this problem, leading to the same final product.

Ge. P.; and Kirk, K.L. *J.Org.Chem.*, **61**, 8671 (1996).

**Exercise 104**

- 1– The alcohol attacks intramolecularly the lactone carbonyl, which has been previously activated by protonation.
- 2– The lactone is opened and a new lactone is formed.
- 3– The liberated hydroxy group reacts with the methyl ester, producing the generation of methanol and the formation of a new lactone.

Rodríguez, C.M.; Martín, T.; and Martín, V.S., *J.Org.Chem.*, **61**, 8448 (1996).

**Exercise 105**

- 1– The lactone is hydrolysed under basic conditions, and the enol tautomerizes to a ketone.
- 2– The resulting  $\beta$ -keto acid suffers a decarboxylation yielding a ketone.
- 3– The alkoxide generated in the opening of the lactone attacks the carbamate carbonyl and expels benzylic alcohol.

Ward, D.E.; Gai, Y.; and Kaller, B.F., *J.Org.Chem.*, **61**, 5498 (1996).

**Exercise 106**

- 1– The protonation of the ethoxy group is followed by the detachment of ethanol and the formation of an acylimonium cation.
- 2– The allene reacts intramolecularly with this cation, producing a vinylic cation that is trapped with iodide.
- 2– The alcohol is formylated by reaction with formic acid under acidic conditions.

Beyersbergen van Henegouwen, W.G.; Fieseler, R.M.; Rutjes, F.P.J.; and Hiemstra, H. *J.Org.Chem.*, **65**, 8317 (2000).

**Exercise 107**

- 1– The *p*-nitrobenzoate is hydrolysed under basic conditions.
- 2– The resulting alkoxide displaces the neighbouring mesylate, yielding an epoxide.
- 3– The amine opens the epoxide by attack on its less hindered side.

Takashi, I.; andamada, Y.; Abe, H.; Sagawa, S.; and Cho, H., *J.Org.Chem.* **65**, 1623 (2000).

**Exercise 108**

- 1– The ammonia displaces the methoxide by an addition-elimination mechanism, yielding a guanidine.
- 2– The primary nitrogen in the guanidine reacts intramolecularly with the ketone, producing an imine.
- 3– The alcohol reacts intramolecularly with the imine yielding the final guanidine, that is protonated due to its very high basicity.

Coffey, D.S.; McDonald, A.I.; Overman, L.E.; Rabinowitz, M.H.; and Renhowe, P.A., *J.Am.Chem.Soc.* **122**, 4893 (2000).

**Exercise 109**

- 1– An imine is formed by condensation of the amine with the aldehyde.
- 2– The alcohol adds intramolecularly to the imine, producing an oxazolidine ring.
- 3– The oxazolidine nitrogen attacks intramolecularly the ester carbonyl and produces the expulsion of methoxide.

Amat, M.; Bosch, J.; Hidalgo, J.; Cató, M.; Pérez, M.; LLor, N.; Molins, E.; Miravittles, C.; Orozco, M.; and Luque, J. *J.Org.Chem.*, **65**, 3074 (2000).

**Exercise 110**

- 1– The primary amine attacks the lactone carbonyl, producing its opening by an addition-elimination mechanism, and yielding an amide.
- 2– The *i*Pr<sub>2</sub>NEt produces the elimination of the benzyloxy group on  $\beta$  to the ketone, by means of an E<sub>1c</sub>B mechanism, producing an  $\alpha,\beta$ -unsaturated ketone.
- 3– The amide nitrogen effects a conjugate addition on the enone.

4– The alcohol attacks the ketone yielding a hemiacetal.

Sóti, F.; Kajtár-Peredy, M.; Kardos-Balogh, Z.; Incze, M.; Keresztury, G.; Czira, G.; and Szántay, Csaba, *Tetrahedron*, **50**, 8209 (1994).

### Exercise 111

1– The osmium tetroxide produces a dihydroxy-addition to the alkene.

2– The concentrated hydrochloric acid causes the hydrolysis of the lactone.

3– A new lactone—this time a  $\gamma$ -lactone—is formed. This lactone does not suffer hydrolysis because of the thermodynamic stability associated with a six-membered ring.

4– The two free alcohols react with acetone under acidic catalysis, producing an acetal.

Oka, T.; and Murai, A., *Tetrahedron*, **54**, 1 (1998).

### Exercise 112

1– Mesyl chloride, in the presence of a base, produces the mesylation of the alcohol.

2– The azide anion displaces the mesylate with inversion of configuration, yielding an organic azide.

3– The catalytic hydrogenation produces the reduction of the azide to an amine.

4– The amine attacks the lactone carbonyl, causing its opening and the formation of a lactam.

Ha, J.D.; and Cha, J.K., *J.Am.Chem.Soc.*, **121**, 10012 (1999).

### Exercise 113

1– The protonation of dimethoxypropane converts one of its oxygen atoms in a good-leaving group. This allows the departure of methanol, resulting in the formation of a cation on  $\alpha$  to an oxygen.

2– This cation is attacked by the alcohol in the starting compound.

3– The resulting acetal loses methanol by a mechanism akin to the one in part 1, giving a cation that is attacked by one of the lactone oxygen atoms.

4– This oxygen takes positive charge and is lost as a leaving-group, when one molecule of methanol attacks the carbonyl group.

Sinha, S.C.; Sinha, S.C.; and Keinan, E., *J.Org.Chem.*, **64**, 7067 (1999).

**Exercise 114**

- 1– The hydrochloric acid produces the lactone hydrolysis.
- 2– The alcohol reacts intramolecularly with the aldehyde, forming a hemiacetal.
- 3– Protonation of the hemiacetal hydroxyl is followed by water loss, resulting in the formation of a cation on  $\alpha$  to an oxygen.
- 4– The carboxylic acid attacks this cation.

Toyota, M.; Hirota, M., Nishikawa, Y.; Fukumoto, K.; and Ihara, M., *J.Org.Chem.*, **63**, 5895 (1998).

**Exercise 115**

- 1– A hydroxide anion attacks the carbonyl, giving a tetrahedral intermediate that may evolve by expulsion of a nitrogen or an oxygen atom.
- 2– The expulsion of a nitrogen atom leads to an amide that reacts intramolecularly with the epoxide, generating two five-membered fused cycles and a monoalkyl carbonate that loses  $\text{CO}_2$ , yielding the first product.
- 3– Alternatively, the expulsion of an oxygen atom yields an alkoxide that attacks intramolecularly the epoxide, producing two seven-membered fused rings and a carbamic acid, that loses  $\text{CO}_2$ , giving the second product.
- 4– A carbamic acid and a monoalkyl carbonate are also formed. Both evolve by releasing carbon dioxide.

White, J.D.; and Hrcniar, P., *J.Org.Chem.*, **65**, 9129 (2000).

**Exercise 116**

- 1– The lactone carbonyl is attacked by the amine, giving an amide through an addition-elimination mechanism with ejection of an enolate.
- 2– The enolate tautomerizes to a ketone.
- 3– The ketone is attacked by the amide nitrogen, producing an  $\alpha$ -aminoalcohol.
- 4– The  $\alpha$ -aminoalcohol loses a hydroxy group, generating an iminium salt.
- 5– The alcohol in the hydroxyethyl group linked to the nitrogen attacks the iminium salt.

Goverdhan, M.; Shailesh, R.; and Venkateswarlu, Y., *Tetrahedron*, **50**, 11729 (1994).

**Exercise 117**

- 1– The catalytic hydrogenation produces the reductive cleavage of both N-O bonds, giving rise to an amine and a hemiacetal.
- 2– The hemiacetal suffers a fragmentation yielding 2-phenylcyclohexanol and an aldehyde.
- 3– The amine reacts intramolecularly with the aldehyde, producing a cyclic enamine.
- 4– The enamine double-bond is reduced by catalytic hydrogenation, yielding a cyclic amine.
- 5– The resulting amine reacts intramolecularly with the methyl ester, producing a lactam.

Denmark, S.E.; Hurd, A.R.; and Sacha, H.J., *J.Org.Chem.*, **62**, 1668 (1997).

**Exercise 118**

- 1– Acidic hydrolysis of the epoxide produces a diol.
- 2– Acidic hydrolysis of the ketene dithioacetal generates a carboxylic acid.
- 3– A  $\gamma$ -lactone is formed by reaction between the carboxylic acid and the primary alcohol.
- 4– The tertiary alcohol is dehydrated, probably via a very stabilized benzylic tertiary carbocation.

The epoxide hydrolysis happens by water attack on the more substituted carbon of the protonated epoxide. An E1 mechanism is also possible via a strongly stabilized tertiary carbocation.

The hydrolysis of the ketene dithioacetal happens through the following steps:

- 1– Protonation of the alkene with formation of a cation stabilized by both sulfur atoms.
- 2– Water attack on the cation, with formation of an intermediate with a carbon linked to two sulfur and one oxygen atoms.
- 3– Expulsion of a sulfur with formation a thioester.
- 4– Hydrolysis of the thioester through a normal mechanism of addition-elimination to a carbonyl group.

Matsumoto, T.; Sohma, T.; Andamaguchi, H.; Kurata, S.; and Suzuki, K., *Tetrahedron*, **51**, 7347 (1995).

**Exercise 119**

- 1– The catalytic hydrogenation removes the Cbz protecting group.
- 2– The resulting amine attacks the ketone, producing an  $\alpha$ -amino alcohol, and one of the ester groups, generating a lactam.
- 3– The  $\alpha$ -aminoalcohol hydroxy group attacks the other ester, forming a lactone.

- 4– The electron pair of one of the nitrogen atoms produce the opening of the lactone, with the expulsion of a carboxylate and formation of an iminium salt.
- 5– The iminium salt is attacked by methanol.

Domínguez, M.J.; García-López, M.T.; and González-Muñiz, *Tetrahedron*, **48**, 4231 (1992).



# Chapter 4

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## Conjugated Additions to Electron-Deficient Alkenes

### Exercise 120

1– The base DBU forms an alkoxide that adds intramolecularly in a conjugated way to the unsaturated lactone.

Mukai, C.; Hirai, S.; and Hanaoka, M., *J.Org.Chem.*, **62**, 6619 (1997).

### Exercise 121

1– Potassium carbonate acts as a base by producing the abstraction of a proton on an  $\alpha$  position of the cyclopentanone carbonyl. The resulting anion evolves by expulsion of the alkoxide in the  $\beta$  position by an  $E_{1c}B$  mechanism.

McMorris, T; Andu, J.; and Hu, Y., *J.Org.Chem.*, **62**, 3015 (1997).

### Exercise 122

This is a simple case of a double conjugate addition of ammonia to a dienone.

Fields, J.; and Heathcock, C.H., *J.Org.Chem.*, **64**, 8263 (1999).

### Exercise 123

The unsaturated ester suffers a conjugated attack of ammonia, which also displaces the mesylate.

Thompson, D.K.; Hubert, C.N.; and Wightman, R.H., *Tetrahedron*, **49**, 3827 (1993).

**Exercise 124**

- 1– The fluoride anion attacks the silicon atom, producing the alcohol desilylation.
- 2– The resulting alkoxide attacks intramolecularly in a conjugated way the unsaturated ester.

Honda, T.; and Ishikawa, F. *J.Org.Chem.*, **64**, 5542 (1999).

**Exercise 125**

- 1– The base generates an alkoxide that attacks the benzaldehyde, giving a tetrahedral intermediate with a negatively charged oxygen.
- 2– This negatively charged oxygen adds intramolecularly to the unsaturated ester in a conjugated manner.

Claffey, M.M.; Hayes, C.J.; and Heathcock, C.H., *J.Org.Chem.*, **64**, 8267 (1999).

**Exercise 126**

- 1– The triethylamine generates a carbanion on  $\alpha$  to the ketone, which evolves by an  $E_{1cB}$  mechanism, expelling a carboxylate.
- 2– The ketone tautomerizes to the enol form, which in this case is more stable because of extended conjugation.

Clive, D.L.J.; Coltart, D.M.; and Zhou, Y., *J.Org.Chem.*, **64**, 1447 (1999).

**Exercise 127**

- 1– The trimethyl phosphonoacetate anion reacts with the aldehyde in equilibrium with the  $\alpha$ -amino alcohol, giving an unsaturated ester.
- 2– The nitrogen of the liberated sulfonamide, after being deprotonated, effects a conjugate addition on the unsaturated ester.

Hart, B.P.; and Rapoport, H., *J.Org.Chem.*, **64**, 2050 (1999).

**Exercise 128**

- 1– A conjugate addition of the Grignard reagent to the enone produces an anion.

2– This anion evolves by elimination of the alkoxide on the  $\beta$  position, with recovery of the enone moiety.

Lin, X.; Kavash, R.W.; and Mariano, P.S. *J.Org.Chem.*, **61**, 7335 (1996).

### Exercise 129

1– The *p*-quinone suffers the conjugate addition of acetate.

2– Both ketones in the resulting cyclohexenedione tautomerize to the enol form, yielding an aromatic system.

Radeke, H.S.; Digits, C.A.; Bruner, S.D.; and Snapper, M.L., *J.Org.Chem.*, **62**, 2823 (1997).

### Exercise 130

1– The potassium carbonate generates an alkoxide by deprotonation of the propargyl alcohol.

2– Conjugated addition of the alkoxide to the enone gives a carbanion that adds intramolecularly in a conjugated way to the propargyl ester.

Paquette, L.A.; Tae, J.; Arrington, M.P.; and Sadoun, A.H., *J.Am.Chem.Soc.*, **122**, 2742 (2000).

### Exercise 131

1– The lithium hydroxide hydrolyses the acetate, producing an alkoxide.

2– The unsaturated lactone suffers an intramolecular conjugated addition by the alkoxide.

Blay, G.; Bargues, V.; Cardona, L.; García, B.; and Pedro, J., *J.Org.Chem.*, **65**, 6703 (2000).

### Exercise 132

1– The base generates an amide enolate.

2– The oxygen on the  $\beta$  position is eliminated through an E<sub>1c</sub>B mechanism.

3– The resulting enolate is protonated during the elaboration.

Martin, S.F.; Benage, B.; Geraci, L.S.; Hunter, J.E.; and Mortimore, M., *J.Am.Chem.Soc.*, **113**, 6161 (1991).

**Exercise 133**

- 1– The vinyl lithium compound attacks the lactone carbonyl, causing the expulsion of an alkoxide.
- 2– The alkoxide attacks the alkene in the vinyl sulfone. Nucleophilic attacks on this alkene are easy because of its sulfone-induced electron-deficiency.
- 3– The resulting carbanion is protonated during the elaboration.

Carretero, J.C.; de Diego, J.E.; and Hamdouchi, C., *Tetrahedron*, **55**, 15159 (1999).

**Exercise 134**

- 1– The strong base LHMDS generates an anion on  $\alpha$  to the ketone.
- 2– A conjugated addition of this anion to the unsaturated ester leads to an ester enolate.
- 3– This ester enolate effects a conjugate addition to the enone.

Ihara, M.; Makita, K.; and Takasu, K., *J.Org.Chem.*, **64**, 1259 (1999).

**Exercise 135**

- 1– The carbonyl oxygen attacks the triflic anhydride, producing a strong activation of the ketone.
- 2– This strong activation allows the nucleophilic attack of an alkene, producing a vinyl triflate, a cyclopropane and a carbocation.
- 3– A proton departure produces the formation of an alkene.

The bis-1,8-(dimethylamino)naphthalene, also called proton sponge® works as an amine with an exceptional basicity and very limited nucleophilicity.

Snider, B.B.; Vo, N.H.; and O'Neil, S.V., *J.Org.Chem.*, **63**, 4732 (1998).

**Exercise 136**

- 1– The base LHMDS forms a lactone enolate.
- 2– The expulsion of an alkoxide by a retro-conjugated addition leads to the tetrahydrofuran opening.
- 3– The resulting alkoxide reacts intramolecularly with the ester carbonyl, producing a trans-acylation.

Mukai, C.; Moharram, S.M.; Azukizawa, S.; and Hanaoka, M., *J.Org.Chem.*, **62**, 8095 (1997).

**Exercise 137**

- 1– The base abstracts a proton from one of the  $\alpha$  positions of the ketone.
- 2– The resulting anion evolves by expulsion of one of the dioxolane oxygen atoms, leading to the formation of an enone and a hemiacetal.
- 3– Detachment of acetone yields the final compound.

Barros, M.T.; Maycock, C.D.; and Ventura, M.R., *J.Org.Chem.*, **62**, 3984 (1997).

**Exercise 138**

- 1– The sodium hydride generates an anion on the indole nitrogen.
- 2– This anion reacts with the alkene in the dimethyl vinyl sulfonium salt, producing a sulfur ylide.
- 3– This ylide reacts intramolecularly with the aldehyde, yielding an alkoxide that displaces the positively charged sulfur atom, resulting in the formation of an epoxide.

Wang, Z.; and Jimenez, L.S., *J.Org.Chem.*, **61**, 816 (1996).

**Exercise 139**

- 1– The inone suffers a conjugated addition by the enamine, which attacks by way of its nucleophilic carbon.
- 2– The resulting imine tautomerizes to the corresponding enamine.
- 3– The nitrogen atom condensates intramolecularly with the ketone.

Bagley, M.C.; Bashford, K.E.; Hesketh, C.L.; and Moody, C.J., *J.Am.Chem.Soc.*, **122**, 3301 (2000).

**Exercise 140**

- 1– The triethylamine generates an anion on the amide nitrogen.
- 2– There is a conjugated addition of this nitrogen atom on the unsaturated ester, giving an ester enolate.
- 3– A conjugated intramolecular addition of this ester enolate on the unsaturated amide gives the final compound.

Mekouar, K.; Génisson, Y.; Leue, S.; and Greene, A.E. *J.Org.Chem.*, **65**, 5212 (2000).

**Exercise 141**

- 1– The acetal is hydrolysed under acidic conditions, giving a hemiacetal.
- 2– The hemiacetal equilibrates with a hydroxyenal.
- 3– An intramolecular conjugate addition of the alcohol on the enal yields the final compound.

Yu, P.; Wang, T.; and Cook, J.M., *J.Org.Chem.*, **65**, 3173 (2000).

**Exercise 142**

- 1– Sodium hydride forms an anion on the indole nitrogen.
- 2– This anion attacks the alkene in the vinyl phosphonium salt, producing an anion on  $\alpha$  to the positively charged phosphorous atom. The resulting intermediate is a Wittig ylide. This attack is akin to a conjugated attack to an  $\alpha,\beta$ -unsaturated carbonyl compound, and happens thanks to the electron-deficiency of the alkene in the vinyl phosphonium salt and the stability of the resulting carbanion.
- 3– The Wittig ylide attacks intramolecularly the aldehyde, yielding an alkene.
- 4– Two alkenes suffer an isomerization through a base-catalysed deprotonation-protonation, yielding a compound with a greater stability due to the presence of two isolated benzenic and pyrrolic aromatic systems. These two aromatic systems fused as an indole would result in lower aromatic stabilization.

Cotterill, A.S.; Hartopp, P.; Jones, G.B.; Moody, C.J.; Norton, C.L.; O'Sullivan, N.; and Swann, E., *Tetrahedron*, **50**, 7657 (1994).

**Exercise 143**

- 1– The base DBU induces an  $E_{1cB}$  elimination of the sulfone, giving an unsaturated lactone.
- 2– An anion at the  $\gamma$  position of the carbonyl of the unsaturated lactone is formed, leading to the expulsion of one of the alkoxides of the acetal, and the formation of the anion of a hemiacetal.
- 3– This anion evolves producing the evolution of acetone and the formation of an alkoxide.
- 4– The resulting alkoxide attacks the silicon, resulting in a trans-silylation.

Survet, J.; and Vatiè, J., *Tetrahedron*, **55**, 13011 (1999).

**Exercise 144**

This is an example of the so-called Paal-Knorr pyrrole synthesis. Additionally, there is formation of an unsaturated ester, which suffers a conjugated addition. A plausible mechanism is the following one:

- 1– An imine is formed by reaction of benzylamine with the aldehyde.
- 2– The imine tautomerizes to a dienamine, where a diene is conjugated with the ester.
- 3– The nitrogen of the dienamine attacks the ketone, producing an  $\alpha$ -aminoalcohol, which evolves to the pyrrole by dehydration.
- 4– The resulting conjugated ester can, additionally, suffer a conjugated addition of acetic acid, or benzylamine, yielding two other possible compounds.

Fürstner, A.; and Krause, H., *J.Org.Chem.*, **64**, 8281 (1999).

**Exercise 145**

- 1– Cesium carbonate acts as a base by forming an anion on the pyridone nitrogen.
- 2– Conjugate addition of this anion to *tert*-butyl acrylate, results in the formation of an anion on the  $\alpha$  position of the *tert*-butyl ester.
- 3– This anion reacts with the *n*-propyl ester, producing the expulsion of propoxide and the formation of a ketone.
- 4– The ketone tautomerizes to the enol form, which in this case is more stable because of the conjugation of the resulting alkene with an ester.

Henegar, K.E.; Ashford, S.W.; Baughman, T.A.; Sih, J.C.; and Gu, R.-L., *J.Org.Chem.*, **62**, 6588 (1997).

**Exercise 146**

- 1– The methoxide generates a carbanion on ethyl cyanoacetate.
- 2– A conjugated attack of this anion on the alkene produces a carbanion on  $\alpha$  to the ketone, which evolves by expelling methoxide and recovering the alkene moiety.
- 3– Deprotonation of the imide nitrogen yields a tridentate anion.
- 4– This tridentate anion attacks intramolecularly the cyanide, yielding an imine that is hydrolyzed to a ketone.

Pérez, D.; Burés, G.; Guitián, E.; and Castedo, L., *J.Org.Chem.*, **61**, 1650 (1996).

**Exercise 147**

- 1– A carbanion stabilized by both carbonyl groups in ethyl acetoacetate is formed.
- 2– This anion adds in a conjugated way to the unsaturated ester.
- 3– A carbanion stabilised by both carbonyl groups in the  $\beta$ -keto ester is formed. This carbanion reacts intramolecularly with the ester, resulting in the expulsion of methoxide and the formation of a ketone.
- 4– The ester is hydrolysed by potassium hydroxide, yielding a carboxylic acid that suffers decarboxylation by heating in sulfuric acid.

Krohn, K.; Micheel, J.; and Zulowski, M., *Tetrahedron*, **56**, 4753 (2000).

**Exercise 148**

- 1– After protonation of the ketone carbonyl, there is an electronic movement that begins on the electron pair in the dihydrofuran oxygen, produces the cleavage of one of the cyclobutane bonds, and leads to the formation of a dienol. The dienol tautomerizes to an enone.
- 2– The furan ring gains aromaticity by losing a proton.
- 3– The acidic methanolysis of the lactone yields a methyl ester and an alcohol.
- 4– The dehydration of the alcohol under acidic conditions leads to the final compound.

Crimmins, M.T.; Pace, J.M.; Nantermet, P.G.; Kim-Meade, A.S.; Thomas, J.B.; Watterson, S.H.; and Wagman, A.S., *J.Am.Chem.Soc.* **122**, 8453 (2000).

**Exercise 149**

- 1– The acetal is hydrolysed under acidic conditions.
- 2– The fluoride anion produces the cleavage of the silyl ether.
- 3– One of the alcohols adds intramolecularly in a conjugated way to the enone.
- 4– An intramolecular reaction between two of the alcohols and the ketone yields an acetal.

Burke, S.D.; Jung, K.W.; Lambert, W.T.; Phillips, J.R.; and Klovning, J.J., *J.Org.Chem.*, **65**, 4070 (2000).

# Chapter 5

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## Reactions via Enols and Enolates

### Exercise 150

- 1– The enolate of oxalacetic acid condenses with the aldehyde in equilibrium with the hemiacetal.
- 2– The sulfur attacks the ketone.

Mack, H.; and Brossmer, R., *Tetrahedron*, **54**, 4521 (1998).

### Exercise 151

- 1– The lithium diisopropylamide abstracts a proton from the  $\gamma$  position of the ester carbonyl. This proton is acidic because of the extended delocalization of the conjugated base.
- 2– The resulting anion attacks the benzaldehyde, producing an alkoxide that displaces intramolecularly the methoxide group in the ester.

Schlessinger, R.H.; and Pettus, L.H., *J.Org.Chem.*, **63**, 9089 (1998).

### Exercise 152

- 1– The oxygen in the enol form of the aldehyde attacks intramolecularly the epoxide, which is previously activated by protonation by *p*-toluenesulfonic acid.
- 2– The resulting tertiary alcohol suffers a dehydration under acidic conditions.

Zoretic, P.A.; Zhang, Y.; and Fang, H., *J.Org.Chem.*, **63**, 1162 (1998).

**Exercise 153**

- 1– The potassium hydroxide abstracts a proton on  $\alpha$  to the ketone. The resulting anion attacks intramolecularly the epoxide, generating an alcohol.
- 2– This alcohol attacks the ketone, producing a hemiacetal.

Johnston, J.N.; Tsui, H.-C.; and Paquette, L.A., *J.Org.Chem.*, **63**, 129 (1998).

**Exercise 154**

- 1– Mesyl chloride, in the presence of triethylamine, produces the mesylation of the carboxylic acid hydroxy group, which thus becomes a good-leaving group.
- 2– The triethylamine generates an anion on  $\alpha$  to the ketone. The oxygen of this ambident anion attacks the mesylated carboxylic acid, producing the final lactone.

Konoike, T.; Okada, T.; and Araki, Y., *J.Org.Chem.*, **63**, 3037 (1998).

**Exercise 155**

- 1– The enol form of the aniline ketone condenses with the pyridine ketone. This produces an alcohol, which suffers dehydration, giving an enone.
- 2– An intramolecular condensation between the amine and a ketone yields an imine.

Henegar, K.E.; Ashford, S.W.; Baughman, T.A.; Sih, J.C.; and Gu, R.-L., *J.Org.Chem.*, **62**, 6588 (1997).

**Exercise 156**

- 1– Potassium *tert*-butoxide in methanol generates methoxide, which attacks the amide carbonyl, producing the expulsion of the indole nitrogen. An indole nitrogen is a much better leaving-group than a nitrogen atom on a normal amine, because the free electron pair on an indole nitrogen is involved in aromaticity.
- 2– The indole nitrogen reacts with the ketone from the resulting  $\alpha$ -keto ester.

Desmaële, D.; Mekouar, K.; and d'Angelo, J., *J.Org.Chem.*, **62**, 3890 (1997).

**Exercise 157**

- 1– The enol form of the aromatic ketone attacks the carbonyl of the protonated ester.

2– The remaining ketone exists mainly as the enol form, for it gives rise to an aromatic  $\alpha$ -piron.

Garey, D.; Ramirez, M.; Gonzales, S.; Wertsching, A.; Tith, S.; Keefe, K.; and Peña, M.R. *J.Org.Chem.*, 61, 4853 (1996).

### Exercise 158

1– The acetate carbonyl is attacked by methoxide, resulting in the formation of methyl acetate and an alkoxide

2– The alkoxide effects a retrograde aldol reaction, producing a ketone and a lactone enolate.

Lange, G.I.; and Organ, M.G., *J.Org.Chem.*, 61, 5358 (1996).

### Exercise 159

1– A Knoevenagel condensation between dimethyl malonate and the ketone produces an dimethyl alkylidenemalonate. The mechanism of this reaction is the standard one in Knoevenagel condensations and can be found in text books on Organic Chemistry.

2– The tertiary alcohol attacks intramolecularly one of the methyl esters producing a lactone.

Takayama, H.; Kurihara, M.; Kitajima, M.; Said, I.M.; and Aimi, N., *Tetrahedron* 56, 3145 (2000).

### Exercise 160

1– After the protonation of the ketone, one of the methyl groups is deprotonated, resulting in the formation of a ketone tautomer with a tetraenol structure.

2– The tetraenol attacks a molecule of protonated formaldehyde, producing the hydroxymethylation on the  $\delta$  position of the ketone.

Observe that there is no dehydration of the tertiary alcohol, in spite of the strongly acidic conditions employed. This dehydration would need the intermediacy of a tertiary carbocation, that would be highly unstable because it would be located  $\alpha$  to a carbonyl group.

Brummond, K.M.; Lu, J.; and Petersen, J., *J.Am.Chem.Soc.* 122, 4915 (2000).

**Exercise 161**

- 1– After the protonation of the lactone carbonyl, one of the bonds in the cyclobutane is broken, causing the formation of a carbocation  $\alpha$  to the tetrahydrofuran oxygen and the enol tautomer of the lactone.
- 2– The lactone enol tautomer isomerizes to the lactone and methanol traps the carbocation.

Crimmins, M.T.; Pace, J.M.; Nantermet, P.G.; Kim-Meade, A.S.; Thomas, J.B.; Watterson, S.H.; and Wagman, A.S., *J.Am.Chem.Soc.* **122**, 8453 (2000).

**Exercise 162**

- 1– The ketone tautomerizes to an enol.
- 2– The ester carbonyl is activated by complexation with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , so that an intramolecular attack of the enol hydroxy group on the ester carbonyl is possible and produces the expulsion of methoxy and the formation of an unsaturated lactone.

Jacobi, P.A.; and Lee, K., *J.Am.Chem.Soc.*, **122**, 4295 (2000).

**Exercise 163**

- 1– There is an intramolecular Diels-Alder reaction between the enal and the diene.
- 2– The triethylamine transforms the ketone in an enolate that attacks the aldehyde.

Bélangier, G.; and Deslongchamps, P., *J.Org.Chem.*, **65**, 7070 (2000).

**Exercise 164**

- 1– The carbonate abstracts the proton that is located on a benzylic position and on  $\alpha$  to one of the ketones.
- 2– The resulting enolate attacks intramolecularly the other ketone, resulting in the formation of one of the products.

Alternatively, the base may abstract a proton on a homobenzylic position and  $\alpha$  to the other ketone. The resulting enolate may attack the remaining ketone, resulting in the formation of the other possible product.

Krohn, K.; Bernhard, S.; Flörke, U.; and Hayat, N., *J.Org.Chem.*, **65**, 3218 (2000).

**Exercise 165**

- 1– The DABCO makes a conjugated addition to the methyl acrylate, producing an ester enolate and an ammonium salt.
- 2– The ester enolate attacks the aldehyde.
- 3– The ammonium salt is expelled by means of an E<sub>1c</sub>B mechanism, causing the recovery of the alkene conjugated with the ester.

Of course, the mechanism does not begin by abstraction of the proton at the methyl acrylate on an  $\alpha$  position. This proton lacks sufficient acidity, because the corresponding anion is not able to enter into conjugation with the ester carbonyl. This happens because the anion occupies an orbital, which is perpendicular to the p orbitals of the carbonyl group.

Jenn, T.; and Heissler, D., *Tetrahedron*, **54**, 107 (1998).

**Exercise 166**

- 1– Sodium hydride acts as a base, producing a carbanion stabilized by both carbonyls.
- 2– The resulting anion displaces the chloride of a neighbouring molecule.
- 3– Another carbanion stabilized by two carbonyl groups is formed. This carbanion displaces intramolecularly a chloride atom.

Ohshima, T.; Kagechika, K.; Adachi, M.; Sodeoka, M.; and Shibasaki, M., *J.Am.Chem.Soc.*, **118**, 7108 (1996).

**Exercise 167**

- 1– Piperidine induces a Knoevenagel condensation between the  $\alpha$ -keto sulfone and the benzaldehyde, giving a  $\alpha,\beta$ -unsaturated ketone.
- 2– A phenoxide is formed, and it adds intramolecularly in a conjugated fashion to the enone.
- 3– Elimination of methanesulfinic acid is produced, by means of a E<sub>1c</sub>B mechanism, producing again an enone.

Pirrung, M.C.; and Lee, Y.R., *J.Am.Chem.Soc.*, **117**, 4814 (1995).

**Exercise 168**

- 1– A mixed anhydride is formed by reaction of the carboxylic acid with acetic anhydride. Thus, the hydroxyl of the carboxylic is converted in a good-leaving group.
- 2– The enone tautomerizes to the corresponding dienol. This transformation is favoured by the

resulting diene being conjugated with one of the mixed anhydride carbonyl groups.

3– The dienol hydroxyl attacks one of the mixed anhydride carbonyls, producing the expulsion of the acetate.

Boger, D.L.; and Takahashi, K., *J.Am.Chem.Soc.*, **117**, 12452 (1995).

### Exercise 169

Apparently, this reaction could be a simple aldol condensation between the  $\alpha$  position of an ester carbonyl group and an aldehyde. The simultaneous hydrolyses of one of the ester groups shows that a more complicated mechanism is operating. This is one example of the so-called Stobbe condensation, in which an intermediate lactone is formed by attack of a hydroxyl on an ester. Afterwards, the lactone carboxyl acts as a good-leaving group, producing an alkene, and resulting in the overall hydrolyses of one of the ester groups. The detailed mechanism is the following one:

1– Sodium methoxide generates an anion at the  $\alpha$  position of one of the esters of dimethyl succinate.

2– The resulting enolate attacks the aldehyde, generating an alkoxide that reacts with one of the esters, producing a five-membered lactone.

3– An anion on  $\alpha$  to the remaining ester carbonyl is formed. This anion evolves by carboxylate elimination through an  $E_{1c}B$  mechanism.

White, J.D.; Hrcnciar, P.; and Stappenbeck, F., *J.Org.Chem.*, **64**, 7871 (1999).

### Exercise 170

1– Potassium *tert*-butoxide forms an  $\alpha$ -anion at the amide carbonyl.

2– This anion attacks the ketone.

3– The amide nitrogen attacks intramolecularly the ester carbonyl, producing the displacement of methoxide and the formation of a five-membered ring.

Faul, M.M.; Winneroski, L.L.; and Krumrich, C.A., *J.Org.Chem.*, **64**, 2465 (1999).

### Exercise 171

1– The base DBU abstracts a proton placed between both ketones.

2– One of the enolate oxygens attacks the ester carbonyl and expels a methoxide.

3– The remaining ketone tautomerizes, producing a pyrone ring.

Oikawa, H.; Kobayashi, T.; Katayama, K.; Suzuki, Y.; and Ichihara, A., *J.Org.Chem.*, **63**, 8748 (1998).

### Exercise 172

1– The potassium *tert*-butoxide takes a proton from the most acidic  $\alpha$  position of the ketone, which is the one with an aryl attached.

2– The resulting anion effects a conjugate addition to methyl acrylate.

3– An anion on the methyl group attacked to the ketone is formed. This anion attacks intramolecularly the ester group, producing the displacement of ethoxide.

Majetich, G.; Liu, S.; Fang, J.; Siesel, D.; and Zhang, Y., *J.Org.Chem.*, **62**, 6928 (1997).

### Exercise 173

Of course, the mechanism does NOT consist in the direct abstraction of the vinylic proton located on  $\alpha$  to the ketone, giving a vinyl anion that would be methylated. This proton lacks acidity since the corresponding anion would fail to be stabilized by conjugation with the carbonyl group. Resonance stabilization of this anion would not be possible because it would be located on an orbital orthogonal to the  $\pi$  system of the carbonyl group.

A more indirect mechanism operates:

1– The sodium hydride abstracts a proton on an allylic position on  $\gamma$  to the enone, producing an anion with extended delocalization between positions  $\alpha$  and  $\gamma$ .

2– Methyl iodide alkylates this delocalized anion on position  $\alpha$ , generating a ketone with  $\beta,\gamma$ -unsaturation.

3– The alkene migrates into conjugation with the carbonyl group by deprotonation on  $\alpha$ , followed by protonation on  $\gamma$ .

An, J.; and Wiemer, D.F. *J.Org.Chem.*, **61**, 8775 (1996).

### Exercise 174

1– Both the enamine and the oxazolidine are hydrolysed under the acidic aqueous conditions, yielding an aldehyde and a ketone.

2– The enolic form of the methyl ketone reacts intramolecularly with the aldehyde, giving a cyclohexenone, after dehydration of the intermediate  $\beta$ -hydroxy ketone.

Waterson, A.G.; and Meyers, A.I., *J.Org.Chem.*, **65**, 7240 (2000).

### Exercise 175

1– After protonation, the epoxide opens, giving a cation on  $\alpha$  to an oxygen atom. This cation is trapped with water.

2– After protonation of the ketone carbonyl, there is an electronic movement, which begins on the tetrahydrofuran oxygen, leads to the breakage of one of the cyclobutane bonds, and yields an enol that tautomerizes to a ketone.

3– This electronic movement also generates a carbocation on  $\alpha$  to the tetrahydrofuran oxygen, which is trapped with water.

Crimmins, M.T.; Pace, J.M.; Nantermet, P.G.; Kim-Meade, A.S.; Thomas, J.B.; Watterson, S.H.; and Wagman, A.S., *J.Am.Chem.Soc.* **122**, 8453 (2000).

### Exercise 176

1– This reaction is a Favorskii transposition followed by a basic elimination of HBr. It begins with the formation of an anion on  $\alpha$  to the ketone, which displaces one of the bromine atom, giving a cyclopropanone.

2– The methoxide attacks the cyclopropanone carbonyl, and the tetrahedral intermediate evolves by expulsion of a carbanion stabilized by the ester carbonyl, with opening of the cyclopropanone ring.

3– The basic elimination of HBr leads to an alkene, which is stabilized by conjugation with two esters.

White, J.D.; Kim, J.; and Drapela, N.E., *J.Am.Chem.Soc.* **122**, 8665 (2000).

### Exercise 177

1– The silyl ether and the dimethyl acetal are hydrolysed under acidic conditions.

2– The amide nitrogen reacts intramolecularly with the aldehyde, forming an aminal, which loses water under acidic catalysis, producing an acyliminium cation.

3– This cation is trapped intramolecularly by the enolic tautomer of the ketone.

Clive, D.L.J.; and Hisaindee, S. J. *J.Org.Chem.*, **65**, 4923 (2000).

**Exercise 178**

- 1– The methoxide attacks the lactam, producing its opening and the formation of a methyl ester.
- 2– A Dickmann cyclization occurs by attack of an ester enolate on the carbonyl of the other ester, producing  $\beta$ -keto ester.
- 3– The ketone tautomerizes to the enolic form, that in this molecule is the most stable tautomer because of having an alkene conjugated with an ester.

Yu, P.; Wang, T.; and Cook, J.M., *J.Org.Chem.*, **65**, 3173 (2000).

**Exercise 179**

- 1– An anion on  $\alpha$  to one of the ketones and on a benzylic position, attacks the other ketone, producing a six-membered ring.
- 2– An ester enolate attacks one of the ketones, giving a second six-membered cycle.
- 3– This second cycle aromatizes by dehydration of both alcohols and enolization of one of the ketones.

Krohn, K.; Bernhard, S.; Flörke, U.; and Hayat, N., *J.Org.Chem.*, **65**, 3218 (2000).

**Exercise 180**

- 1– The base forms a dianion on diethyl malate, in which one of the charges is on an alkoxide while the other charge is on  $\alpha$  to one of the esters.
- 2– The ester enolate reacts with the imine, yielding a lithium amide.
- 3– This amide attacks intramolecularly one of the esters.

Ahn, J.; Andun, C.; Kim, K.; and Ha, D., *J.Org.Chem.*, **65**, 9249 (2000).

**Exercise 181**

There is a ring contraction via a Favorskii reaction, through the following steps:

- 1– An anion is formed at the  $\alpha$  position of one of the ketones.
- 2– The resulting anion attacks the epoxide, producing its opening and the formation of a cyclopropanone.
- 3– An ethoxide attacks the ketone on the cyclopropanone, leading, by way of an addition-elimination mechanism, to the opening of the three-membered ring, with formation of an ethyl ester and a non-stabilized carbocation.

- 4– This non-stabilized carbocation evolves by formation of an alkene by hydroxide elimination.

Zhu, Jie; Andang, J.-Y.; Klunder, A.; Liu, Z.-Y.; and Zwanenburg, B., *Tetrahedron*, **51**, 5847 (1995).

### Exercise 182

- 1– The anion of dimethyl malonate is formed under the action of sodium methoxide.
- 2– This anion attacks the epoxide, causing its opening and the formation of an alkoxide.
- 3– An attack of the alkoxide on the carbonyl of one of the esters causes the formation of a  $\delta$ -lactone.
- 4– The ester suffers a demethoxycarbonylation under the action of DMSO-H<sub>2</sub>O in the presence of LiCl.

Hedenström, E.; Högberg, H.; Wassgren, A.; Bergström, G.; Löfqvist, J.; Hansson, B; and Anderbrant, O., *Tetrahedron*, **48**, 3139 (1992).

### Exercise 183

- 1– Potassium *tert*-butoxide generates a carbanion on  $\alpha$  to the ester carbonyl.
- 2– The resulting anion attacks the cyanide, producing an imine.
- 3– The imine tautomerizes to the correspondent enamine. This tautomerization is facilitated by the conjugation of the enamine alkene with the ester.
- 4– Potassium *tert*-butoxide produces the elimination of *p*-toluenesulfinic acid (*p*-MePhSO<sub>2</sub>H).

Boger, D.L.; and Takahashi, K., *J.Am.Chem.Soc.*, **117**, 12452 (1995).

### Exercise 184

The PPTS acts as a mild protic acid that catalyzes the formation of the furan, without hydrolysing the *tert*-butyl ester.

- 1– The ketone on  $\beta$  to the ester tautomerizes to the corresponding enol.
- 2– The enol attacks the aldehyde.
- 3– The acetal is hydrolysed, liberating an alcohol that attacks intramolecularly the ketone, giving a hemiacetal.
- 4– Both the hemiacetal hydroxy group and one of the alcohols suffer a dehydration, leading to a furan aromatic ring.

Marshall, J.A.; McNulty, L.M.; and Zou, D., *J.Org.Chem.*, **64**, 5193 (1999).

**Exercise 185**

- 1– The strong base KHMDS generates an anion on  $\alpha$  to the ester carbonyl.
- 2– An unsaturated ester is formed by  $\beta$ -elimination of the silyloxy group by a  $E_{1cB}$  mechanism.
- 3– The base KHMDS forms an anion on  $\gamma$  position of the unsaturated ester.
- 4– This anion, which is delocalized between position  $\alpha$  y  $\gamma$ , attacks by its  $\alpha$  position, producing the displacement of the bromine.

Hart, B.P.; and Rapoport, H., *J.Org.Chem.*, **64**, 2050 (1999).

**Exercise 186**

- 1– The sodium hydride forms an anion on  $\alpha$  to the ketone of the  $\alpha$ -keto amide.
- 2– This anion attacks the ketone of another  $\alpha$ -keto amide molecule.
- 3– An anion on the amide nitrogen is formed.
- 4– This anion attacks intramolecularly another ketone. The resulting aminal is stable due to its location in a five-membered ring, and because the ketone being attacked is particularly reactive since it is placed on  $\alpha$  relative to another carbonyl group.

Snider, B.B.; Song, F.; and Foxman, B.M., *J.Org.Chem.*, **65**, 793 (2000).

**Exercise 187**

- 1– The sodium hydride generates an alkoxide and a ketone enolate.
- 2– The enolate reacts with the 1,1'-carbonyldimidazole, producing the displacement of an imidazole molecule.
- 3– The remaining imidazole is displaced by the alkoxide, which attacks intramolecularly.
- 4– The ketone tautomerizes to the enolic form, which is more stable because of having the alkene conjugated with the lactone carbonyl.

Imidazole works as a good-leaving group because the electron pair on the expelled nitrogen is not a free electron pair as it participates on the aromaticity of imidazole.

Ward, D.E.; Gai, Y.; and Kaller, B.F., *J.Org.Chem.*, **61**, 5498 (1996).

**Exercise 188**

There is a ring contraction by a curious reaction, called Favorskii transposition that occurs via an unstable cyclopropanone.

- 1– Sodium methoxide takes a proton from the carbon atom, located on  $\alpha$  to the ketone, which does not hold a bromine atom. The base can also take a proton from the carbon holding a bromine, which is more acidic, but this leads to an unproductive equilibrium.
- 2– The resulting carbanion displaces intramolecularly the bromine atom, producing a very strained cyclopropanone.
- 3– The cyclopropanone carbonyl is attacked by methoxide, producing a tetrahedral intermediate. This intermediate evolves by opening the ring and expelling a non-stabilized carbanion. The occurrence of a non-stabilized carbanion functioning as leaving group is an exceptional situation, that is possible in this case because of the liberation of strain resulting from the opening of a three-membered ring.
- 4– The non-stabilized carbocation is protonated.

Bai, D.; Xu, R.; Chu, G.; and Zhu, X., *J.Org.Chem.*, **61**, 4600 (1996).

### Exercise 189

- 1– Sodium acetate generates mild basic conditions that allow the deprotonation of the carboxylic acid.
- 2– The resulting carboxylate anion reacts with acetic anhydride producing a mixed anhydride.
- 3– A carbanion on  $\alpha$  to the ketone is formed.
- 4– This anion attacks intramolecularly one of the carbonyl groups of the mixed anhydride, producing the expulsion of acetate.

Liu, J.-H.; andang, Q.-C.; Mal, T.C.W.; and Wong, H.N.C. *J.Org.Chem.*, **65**, 3587 (2000).

### Exercise 190

- 1– The *p*-toluenesulfonic acid generates acidic conditions that allow the protonation of the olefin in the enamine, giving a carbocation stabilized by the nitrogen.
- 2– Methanol attacks this cation.
- 3– Methanol attacks the protonated carbonyl, producing a hemiacetal.
- 4– The amine becomes a good-leaving group by protonation. This allows an electronic movement that begins with the electron pair in the hemiacetal hydroxyl. The resultant electronic motion produces: a) the formation of an ester carbonyl; b) The breakage of a cyclobutane bond; c) The elimination of dimethylamine, with formation of a methyl enol ether.

5– Protonation of the double bond in the methyl enol ether gives a carbocation, which is attacked by methanol. This results in the formation of a dimethyl acetal.

Chen, X-T.; Bhattacharya, S.K.; Zhou, B.; Gutteridge, C.E.; Pettus, T.R.R.; and Danishefsky, S.J., *J.Am.Chem.Soc.*, **121**, 6563 (1999).

### Exercise 191

1– The *p*-toluenesulfonic acid protonates one of the oxygen atoms of the acetal on position 3. The loss of methanol generates a carbocation on  $\alpha$  position relative to an oxygen atom.

2– A water molecule attacks this carbocation, producing a cyclic hemiacetal.

3– The aqueous acidic medium produces the enamide hydrolysis, giving a  $\beta$ -diketone on positions 17–19.

4– An enol tautomer of this  $\beta$ -diketone attacks the carbonyl on position 13.

5– The alcohol on position 11 attacks the ketone on position 19, giving a six-membered cyclic hemiacetal.

Evans, D.A.; Ripin, D.H.B.; Halstead, D.P.; and Campos, K.R., *J.Am.Chem.Soc.*, **121**, 6816 (1999).

### Exercise 192

On first sight, a mechanism based on the attack of the enol form of the ethyl acetoacetate on an iminium cation could be envisioned. The iminium cation could be formed by water lose form the starting  $\alpha$ -aminoalcohol. The following steps would operate.

1– Formation of an iminium cation by water loose form the starting  $\alpha$ -aminoalcohol

2– Attack of the enol form of ethyl acetoacetate on the iminium cation.

3– Intramolecular attack of one of the guanidine nitrogens on the ketone.

4– Dehydration of the resulting  $\beta$ -hydroxy ester.

On the other hand, the use of morpholinium acetate suggests Knoevenagel reaction conditions, with enamine intermediacy. The mechanism would change begging in the second step as follows:

2– An enamine, formed from ethyl acetate and morpholine, attacks the iminium cation.

3– Intramolecular attack of one of the guanidine nitrogens on the resulting iminium cation.

4– Alkene formation by expulsion of protonated morpholine.

Franklin, A.S.; Ly, S.K.; Mackin, G.H.; Overman, L.E.; and Shaka, A.J., M., *J.Org.Chem.*, **64**, 1512 (1999).



# Chapter 6

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## Reactions via Carbanions Stabilized by Functional Groups Other than Carbonyl

### Exercise 193

- 1– The lithium diisopropylamide deprotonates the nitrogen, giving a resonance-stabilized anion. One of the resonant structures of this anion possesses a negative charge on  $\alpha$  to a sulfone.
- 2– This anion reacts with the ester carbonyl, and produces by an addition-elimination mechanism, the expulsion of methoxide.

Back, T.G.; and Nakajima, K., *J.Org.Chem.*, **63**, 6566 (1998).

### Exercise 194

- 1– The base allows the formation of an anion on the  $\alpha$  position of the nitro group.
- 2– The resulting anion attacks one of the aldehydes of glutaraldehyde, giving a  $\beta$ -hydroxy nitro compound.
- 3– A new anion on the  $\alpha$ -position of the nitro group is formed, and the resulting anion attacks intramolecularly the remaining aldehyde.

Luzzio, F.A.; and Fitch, R.W., *J.Org.Chem.*, **64**, 5485 (1999).

### Exercise 195

- 1– The strong base *n*-BuLi generates an allylic anion stabilized by the phosphorous atom and the alkene.
- 2– A conjugate addition of this anion on the unsaturated ester gives an ester enolate.
- 3– The ester enolate displaces intramolecularly the chlorine atom, producing a cyclopropane.

An alternative mechanism in which the initially formed anion loses chlorine, producing a carbene, which adds to the alkene, cannot be discarded. This mechanism seems not to be very probable, as the high reactivity of carbenes seems to contradict the high stereoselectivity of this reaction.

Hanessian, S.; Cantin, L.-D.; and Andreotti, D., *J.Org.Chem.*, **64**, 4893 (1999).

### Exercise 196

- 1– The anion on  $\alpha$  to the isocyanide reacts with the ester, producing the expulsion of methoxide.
- 2– The resulting isocyanide is protonated on its carbon, while there is a deprotonation on  $\alpha$  to the carbonyl group.
- 3– The enolate attacks intramolecularly the carbon atom of the protonated isocyanide.

Ohba, M.; Kubo, H.; and Ishibashi, H., *Tetrahedron* **56**, 7751 (2000).

### Exercise 197

- 1– The BuLi generates an allylic anion that is stabilized by a sulfone.
- 2– This anion displaces the mesylate.
- 3– A new sulfone-stabilized anion is formed and produces the opening of the epoxide by an intramolecular attack, which results in the formation of a cyclopentane.

Miyaoka, H.; Tamura, M.; and Yamada, Y., *Tetrahedron*, **56**, 8083 (2000).

### Exercise 198

- 1– The LDA abstracts the proton on the nitrogen, producing an anion, which delocalizes on  $\alpha$  to the sulfone.
- 2– This anion attacks from the position on  $\alpha$  to the sulfone to the ester carbonyl, leading to the expulsion of methoxide and the formation of a ketone.
- 3– The ketone tautomerizes to the enolic form, resulting in the formation of an aromatic pyrrole ring.

Back, T.G.; and Nakajima, K., *J.Org.Chem.*, **65**, 4543 (2000).

### Exercise 199

- 1– The base generates a carbanion on  $\alpha$  to the cyanide.

- 2– A conjugate addition of this anion to the quinone produces the enolate of one of the ketones.
- 3– This ketone enolate attacks intramolecularly the ester carbonyl, producing a tetrahedral intermediate that evolves by expulsion of alkoxide, resulting in the formation of a cyanhydrine anion.
- 4– This cyanhydrine anion decomposes by expulsion of cyanide, producing the final compound.

Ge, P.; and Russell, R.A., *Tetrahedron*, **51**, 17477 (1997).

### Exercise 200

- 1– An imine is formed by condensation of the amine and the aldehyde, with water withdrawal by azeotropic distillation in benzene.
- 2– The base produces an anion at the  $\alpha$  position of the imine. This carbanion is stabilized by conjugation with the carbon-nitrogen double bond, in a mode closely resembling the stabilization of enolates.
- 3– The carbanion of the  $\alpha$  position of the imine attacks the ester carbonyl group, producing the expulsion of a methoxide by addition-elimination.
- 4– The imine is tautomerized to an enamine, in which the olefin is conjugated with the carbonyl group.

Smith III, A.B.; Benowitz, A.B.; Sprengeler, P.A.; Barbosa, J.; Guzman, M.; Hirschmann, R.; Schweiger, E.J.; Bolin, D.R.; Nagy, Z.; Campbell, R.M.; Cox, D.C.; and Olson, G.L., *J.Am.Chem.Soc.*, **121**, 9286 (1999).