



TWO HUNDRED EXERCISES IN

# Mechanistic Organic Chemistry

*Gabriel Tojo Suárez*



# Two Hundred Exercises in Mechanistic Organic Chemistry



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By

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**Cambridge  
Scholars  
Publishing**



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This book first published 2021

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

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ISBN (10): 1-5275-6397-9

ISBN (13): 978-1-5275-6397-1

To the thousands of synthetic organic chemists preparing new drug candidates who are making our life so much better.



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# PREFACE

Every day thousands of new organic molecules are prepared, mainly for the testing of new medicines. A massive army of synthetic organic chemists laboring in industry and academia executes this task. They play an indispensable role in the progress of health care and save millions of lives. But this enterprise is plagued with obstructions for no synthesis goes according to plan. Yields are meagre, by-products abound and molecules repeatedly prefer to react in unforeseen manners rather than leading to the desired drug candidates. To circumvent this, we must adjust the experimental conditions. The choices are more copious than the sands of Arabia: reagent, solvent, concentration, catalyst, temperature and more. Rather than randomly attempting different permutations, we must put into service an intellectual tool of the greatest efficacy: reaction mechanism. Thus, we may moderate the acidity if it promotes a side-material or reduce the temperature if it leads to decomposition of the product.

But first of all, we must postulate a reaction mechanism. I am deliberately using the verb “postulate” because you need to complete a PhD to ascertain the mechanism of a given reaction. And even with plenty of experiments, a plausible mechanism is little more than a hypothesis not contradicted by facts.

I enjoy the privilege of scrutinizing the dissemination of mechanistic knowledge from start to finish, as I am both a professor of Organic Chemistry and the founder with students of mine of several chemical companies. Thus, eighteen years ago we founded Galchimia, S.A., a company with laboratories in Santiago de Compostela, Madrid and Barcelona that prepares drug candidates for pharmaceutical companies. That is why I know that the present book is very necessary, because organic chemists regularly join synthetic groups in industry without a solid command of **reaction mechanisms**.

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 on 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.

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

No enterprise would meet an end if the goal were perfection. It is better to finish 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 worthwhile even in a very imperfect way, I have written this book. I hope to be proud of this intellectual offspring in spite of its deficiencies.

Santiago, November 11th 2019  
Gabriel Tojo Suárez

## ACKNOWLEDGEMENTS

This book was written twice. At the first attempt, reactions were collected from several highly reputed chemical journals. But, upon asking for copyright permission, I noticed that they could grant you a costless authorization at the outset, to be followed by renewed requests in subsequent editions with uncertain charges. Basically, they would hold hostage future editions of the book for ransom in the form of undetermined copyright fees.

Luckily, open access journals came to the rescue. I want to express my gratitude to the editors of Arkivoc, Beilstein Journal of Organic Chemistry and RCS Advances, as well as to the chemists who publish their research there, with my heartfelt thanks. These journals allow, at least in some articles, to reproduce contents under the Creative Commons Attribution License (CC BY), which authorizes to “remix, transform, and build upon the material for any purpose, even commercially”. Let this and the references included in the Solutions serve as acknowledgement of attribution.

I would like to take the opportunity to recommend to my chemist colleagues to publish their research in open journals. This helps ensure that the maximum of knowledge is available to everyone.

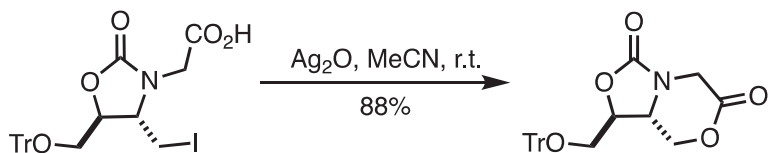
## ABBREVIATIONS

Ac	acetyl, $\text{CH}_3\text{C}(=\text{O})-$
aq.	aqueous
Bn	benzyl, $\text{PhCH}_2-$
Boc	<i>tert</i> -butoxycarbonyl, <i>t</i> -BuOC(=O)-
Bu	<i>n</i> -butyl
<i>i</i> -Bu	isobutyl, $(\text{CH}_3)_2\text{CH}-\text{CH}_2-$
<i>t</i> -Bu	<i>tert</i> -butyl, $\text{Me}_3\text{C}-$
cat.	catalytic
Cbz	benzyloxycarbonyl, BnOC(=O)-
conc.	concentrated
DABCO	4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	<i>p</i> -(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide, $\text{MeS}(=\text{O})\text{Me}$
Et	ethyl, $\text{CH}_3\text{CH}_2-$
KHMDS	$\text{KN}(\text{SiMe}_3)_2$
LHMDS	$\text{LiN}(\text{SiMe}_3)_2$
MCPBA	<i>m</i> -chloroperoxybenzoic acid
Me	methyl, $\text{CH}_3-$
Ms	mesyl, $\text{MeSO}_2-$
NBS	<i>N</i> -bromosuccinimide
Pd/C	palladium on activated carbon
Ph	phenyl
Piv	pivaloyl, $\text{Me}_3\text{CC}(=\text{O})-$
PMB	<i>p</i> -methoxybenzyl, <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> -
PMP	<i>p</i> -methoxyphenyl, <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> -
Py	pyridine
<i>i</i> -Pr	isopropyl, $\text{Me}_2\text{CH}-$
ref.	reflux
r.t.	room temperature
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl, <i>t</i> -BuPh <sub>2</sub> Si-
TBS	<i>tert</i> -butyldimethylsilyl, <i>t</i> -BuMe <sub>2</sub> Si-

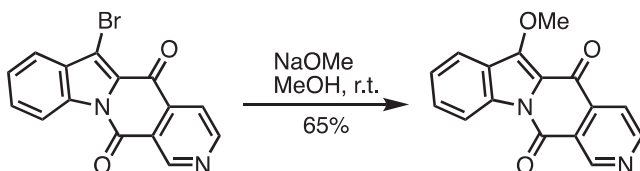
TES	triethylsilyl, Et <sub>3</sub> Si-
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl, Me <sub>3</sub> Si-
Tr	triphenylmethyl (trityl), Ph <sub>3</sub> C-
Ts	<i>p</i> -toluenesulfonyl, <i>p</i> -MeC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> -

# EXERCISES

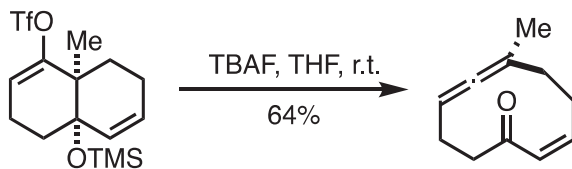
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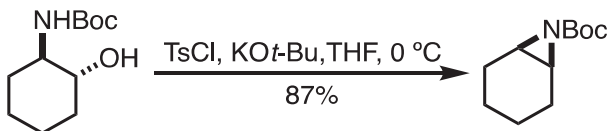
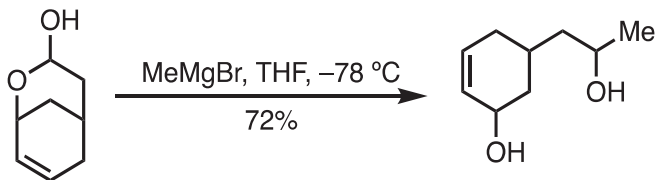
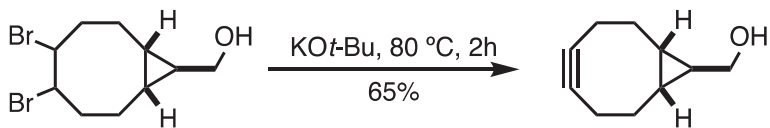


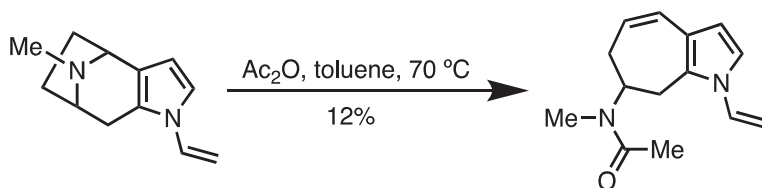
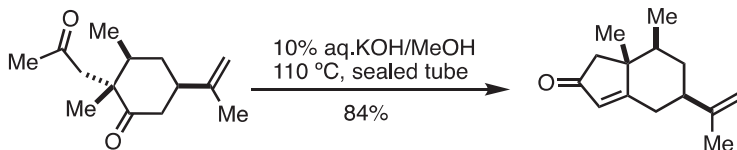
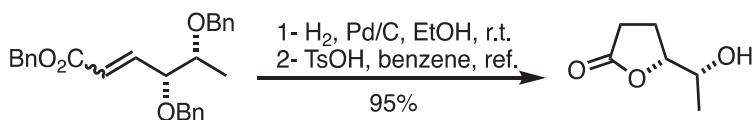
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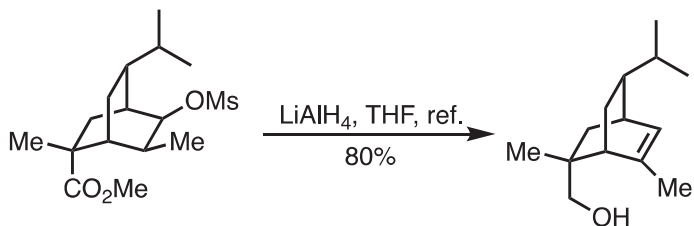
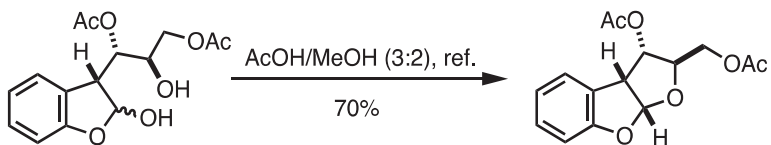
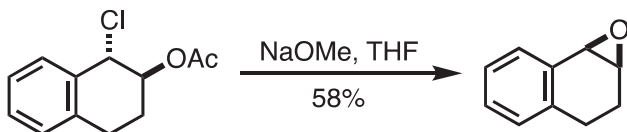
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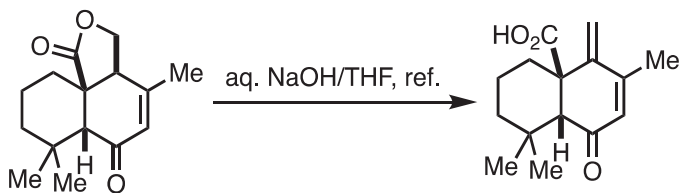
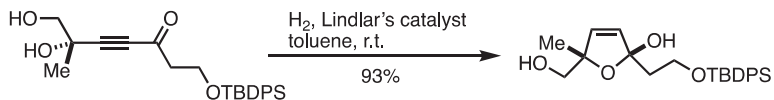
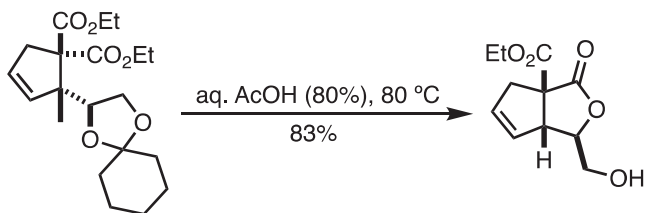


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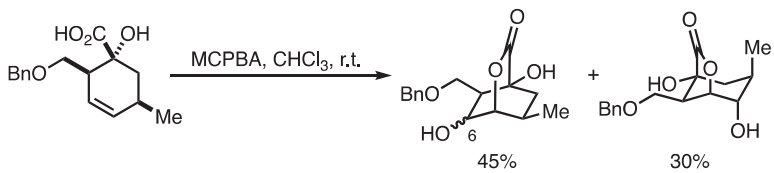
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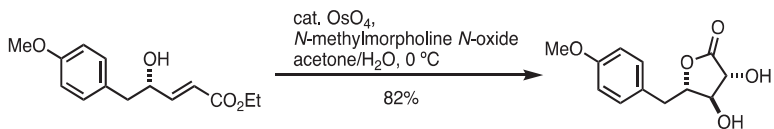
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**Exercise 13****Exercise 14****Exercise 15**

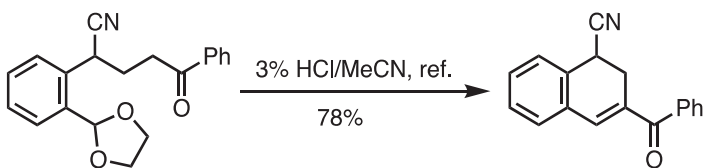
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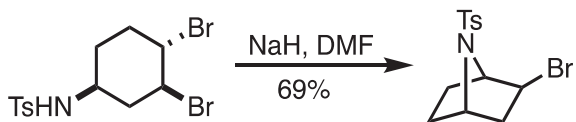
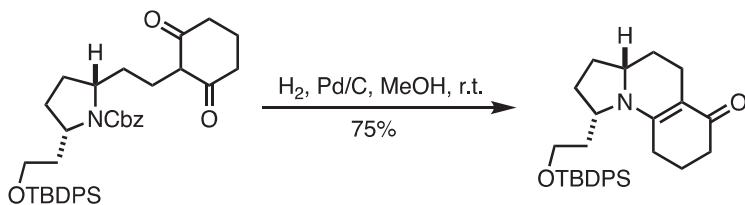


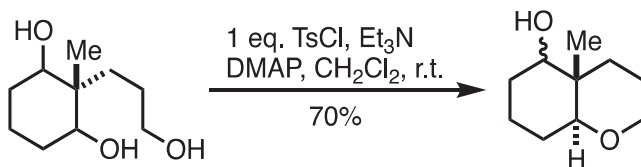
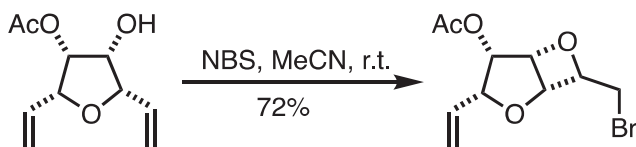
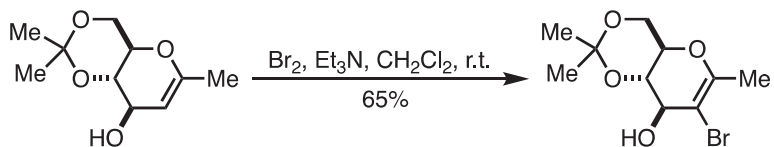
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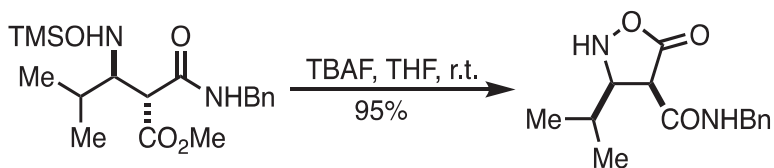
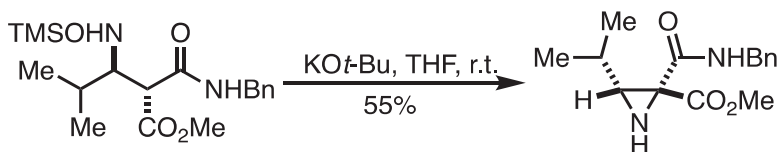
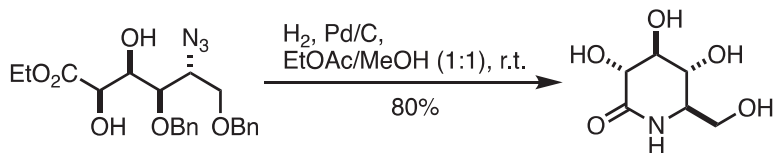


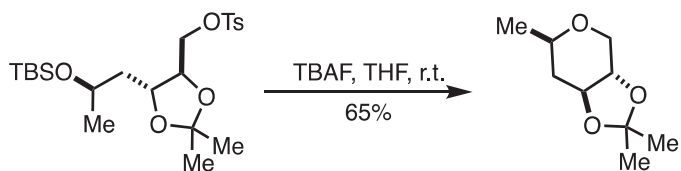
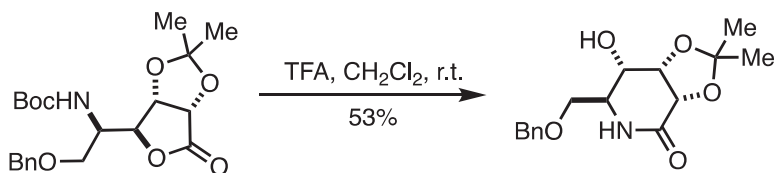
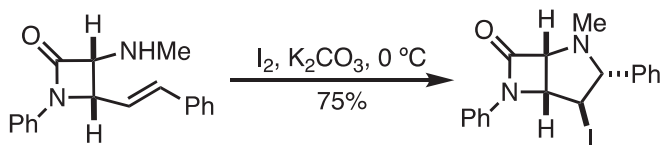
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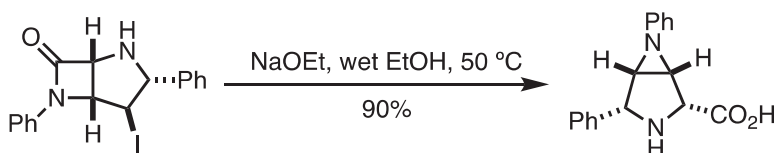
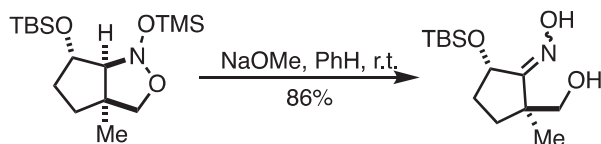
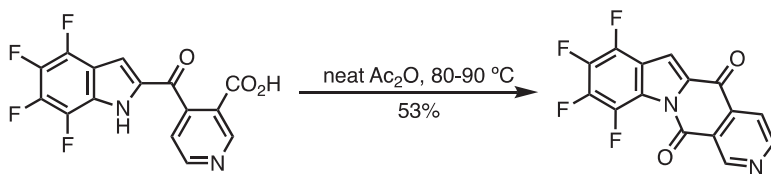


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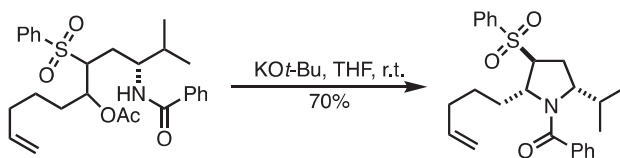
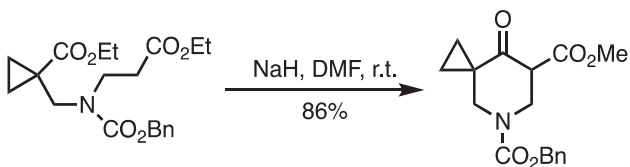
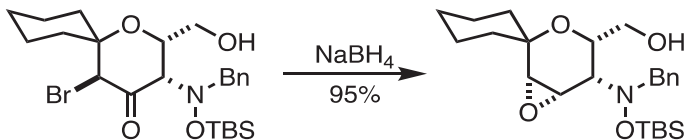
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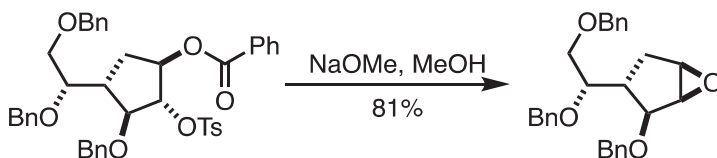
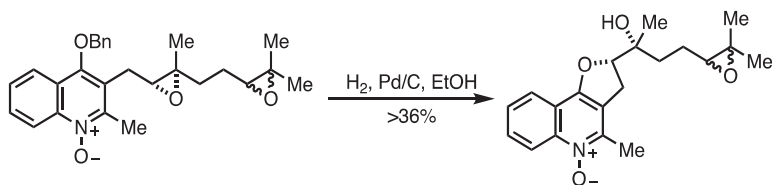
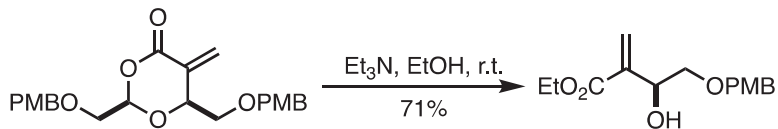
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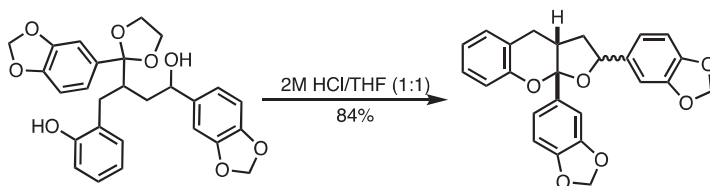
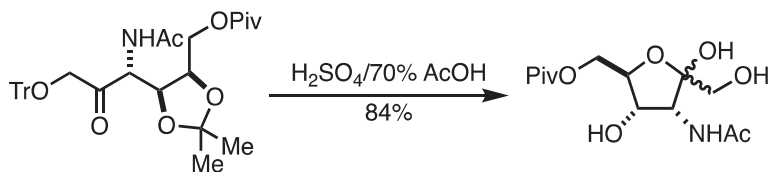
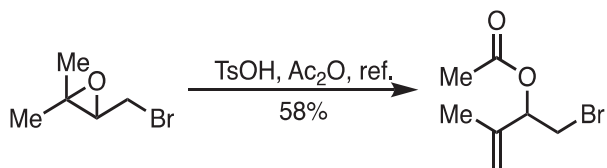
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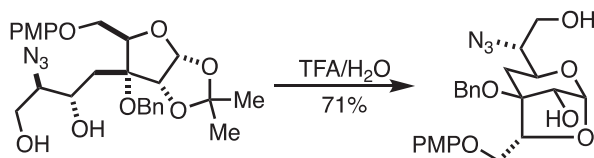
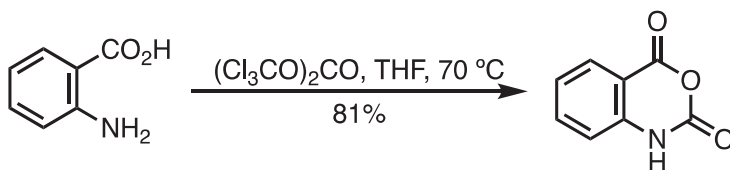
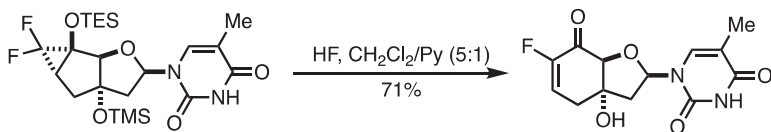
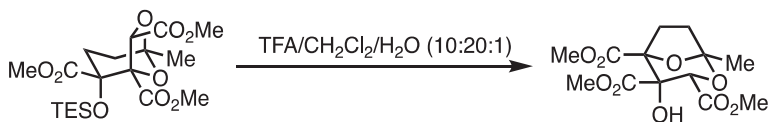
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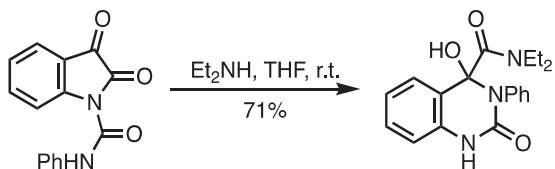
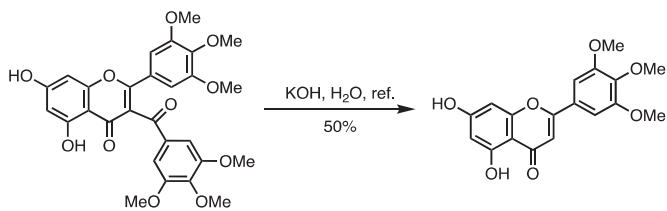
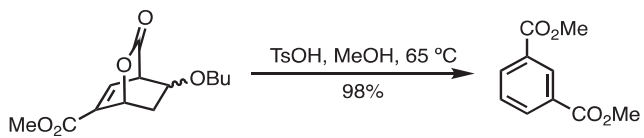


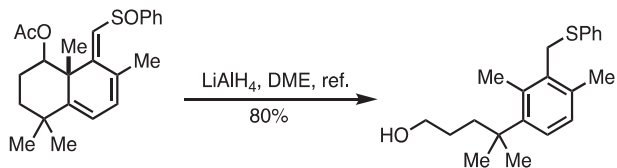
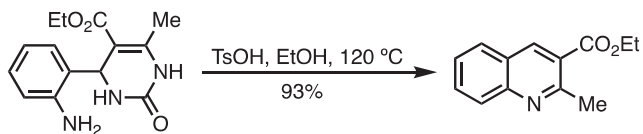
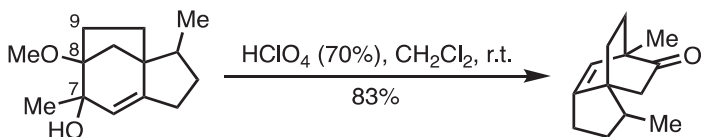
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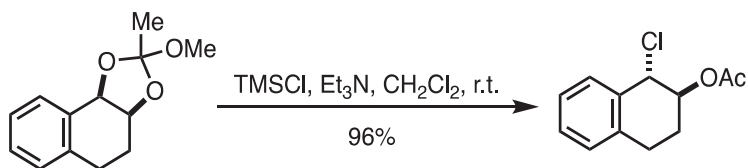
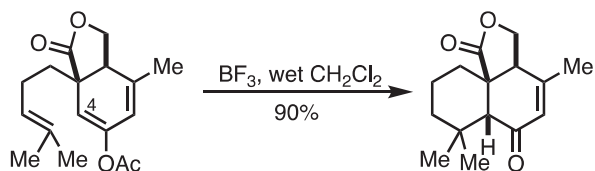
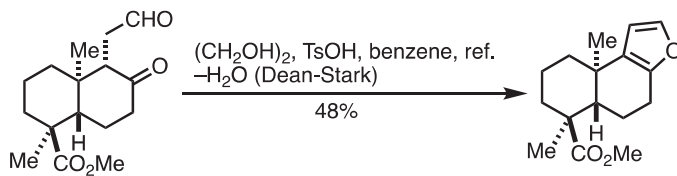
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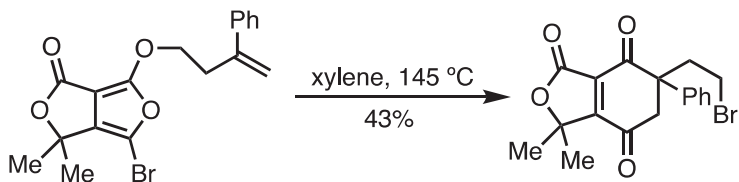
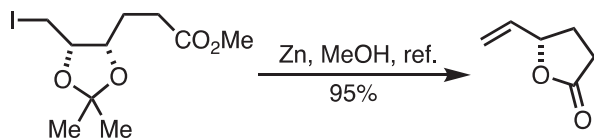
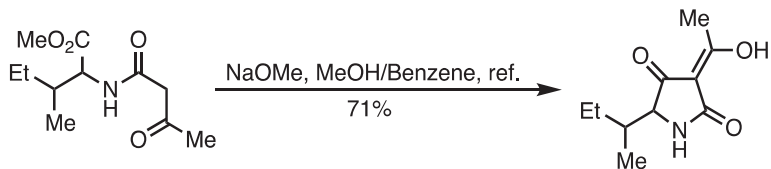
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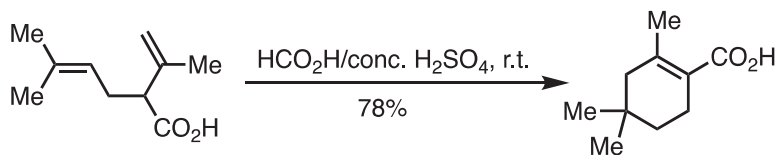
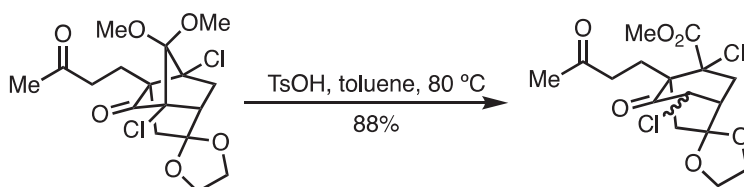
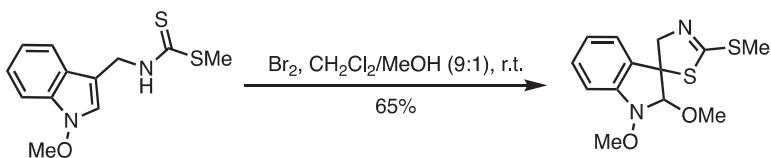
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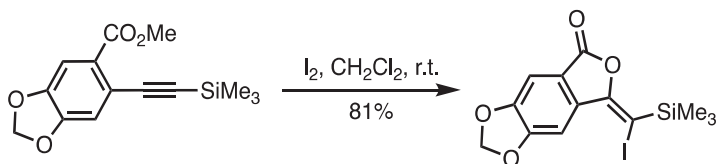
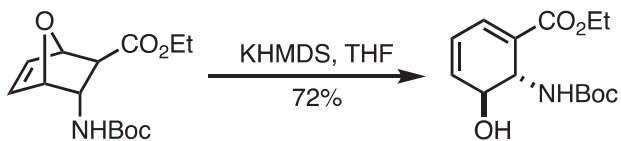
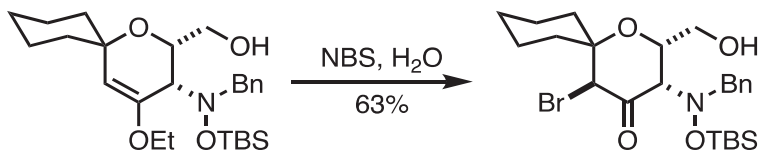
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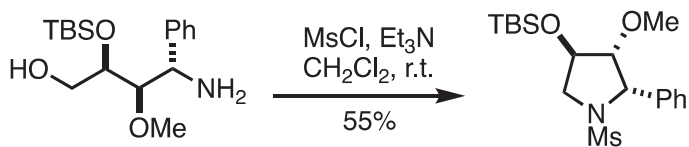
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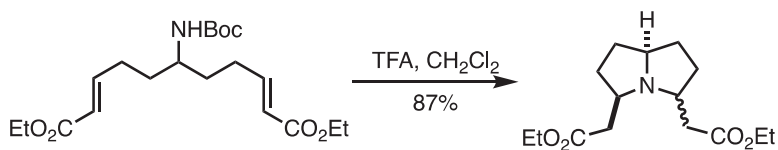
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**Exercise 62****Exercise 63****Exercise 64**

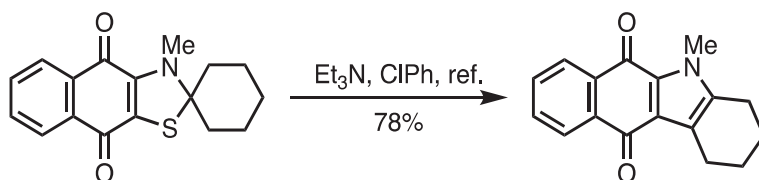
### Exercise 65

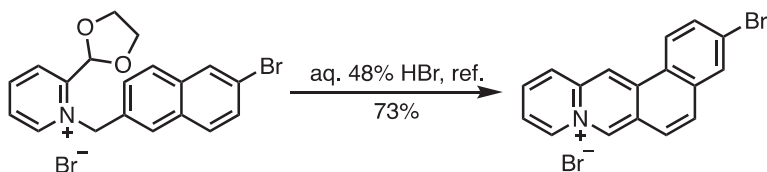
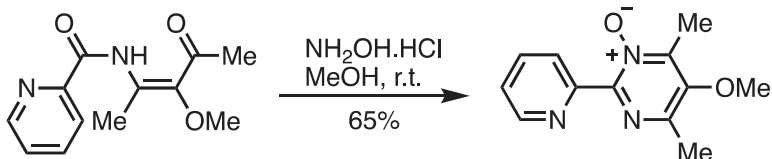
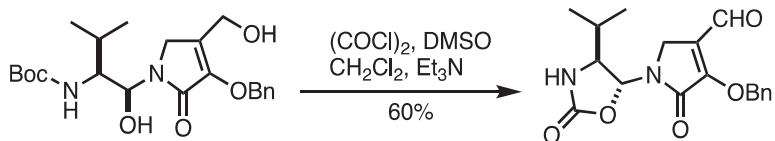
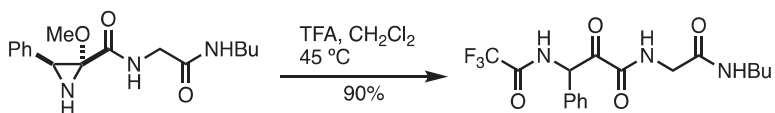


### Exercise 66

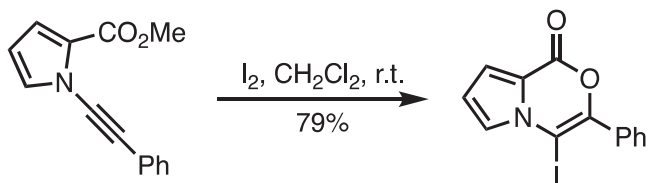


### Exercise 67

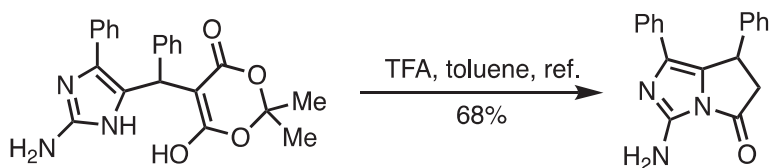


**Exercise 68****Exercise 69****Exercise 70****Exercise 71**

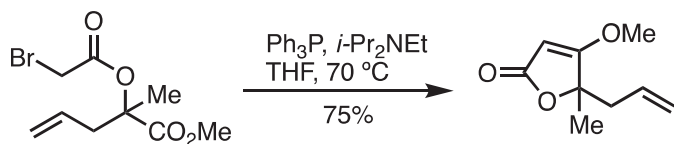
### Exercise 72

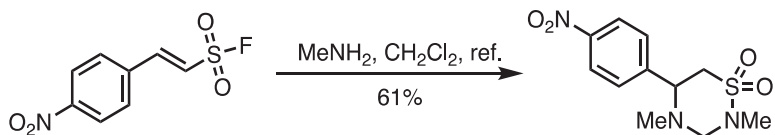
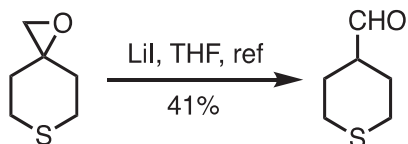
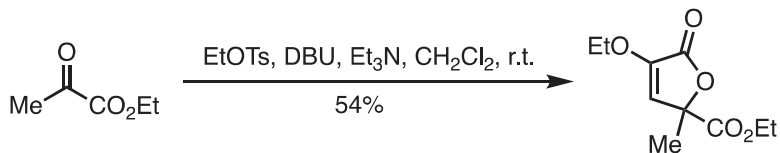


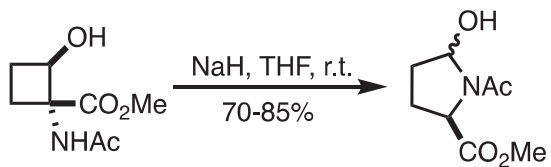
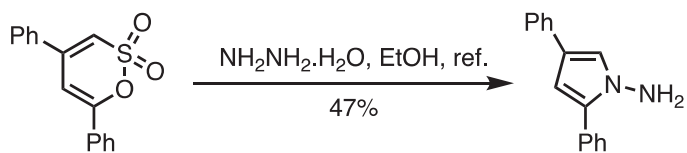
### Exercise 73

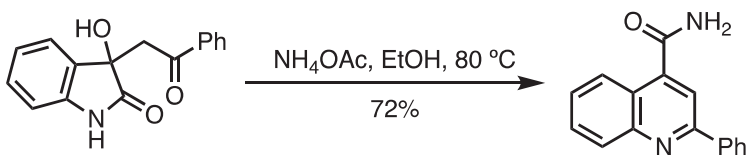
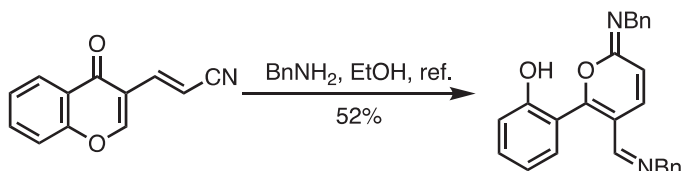
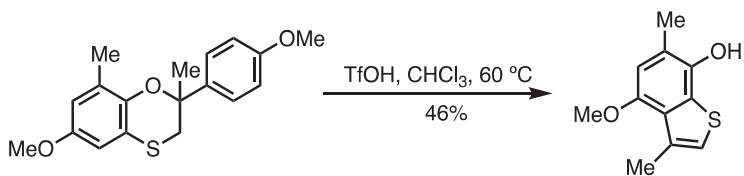


### Exercise 74



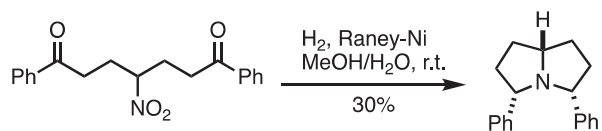
**Exercise 75****Exercise 76****Exercise 77**

**Exercise 78****Exercise 79**

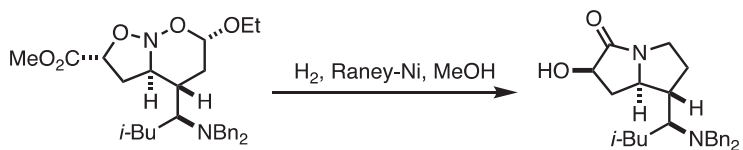
**Exercise 80****Exercise 81****Exercise 82**



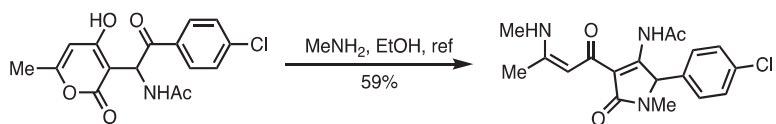
### Exercise 83

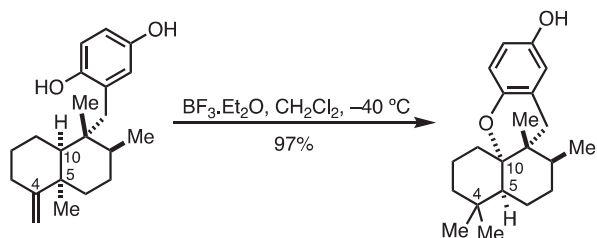
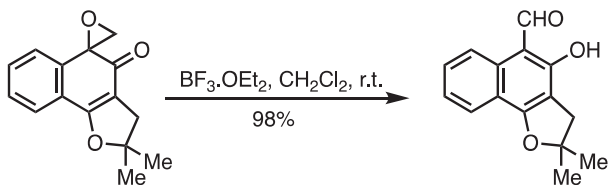
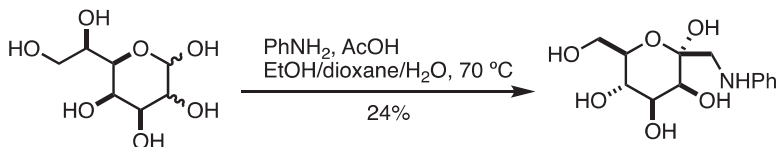


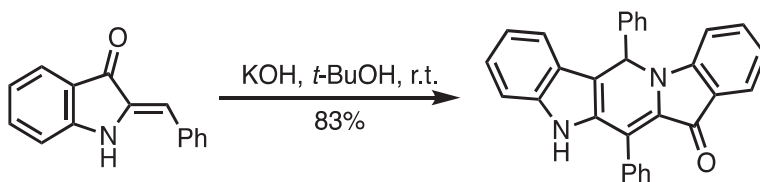
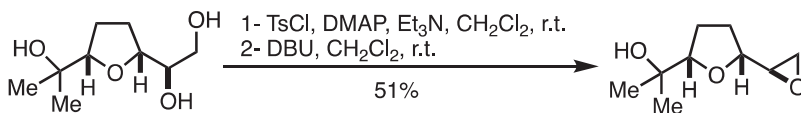
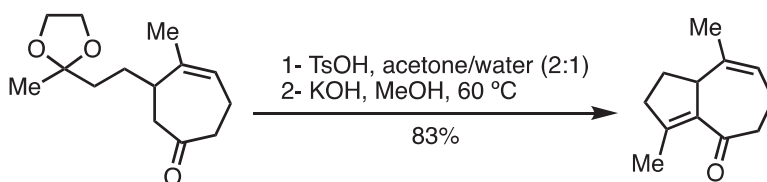
### Exercise 84

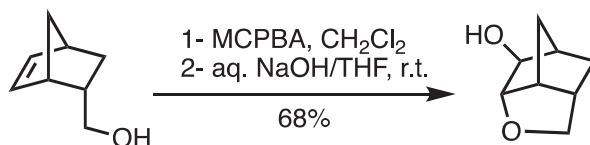
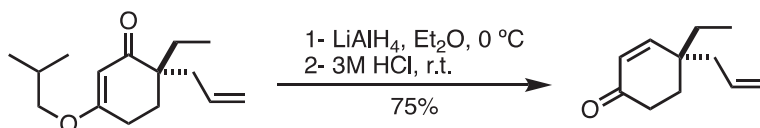
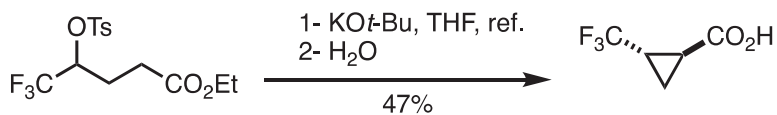


### Exercise 85

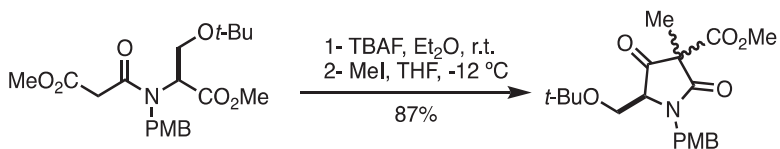


**Exercise 86****Exercise 87****Exercise 88**

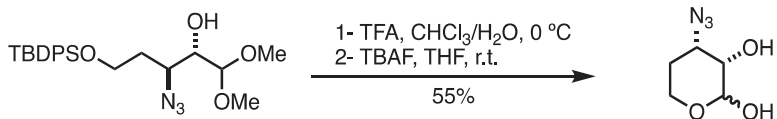
**Exercise 89****Exercise 90****Exercise 91**

**Exercise 92****Exercise 93****Exercise 94**

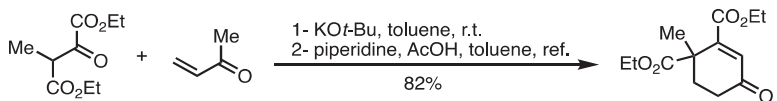
### Exercise 95

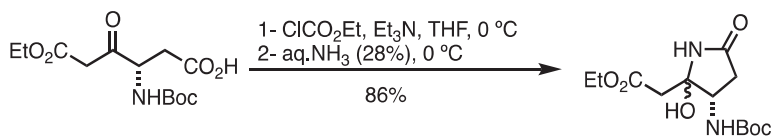
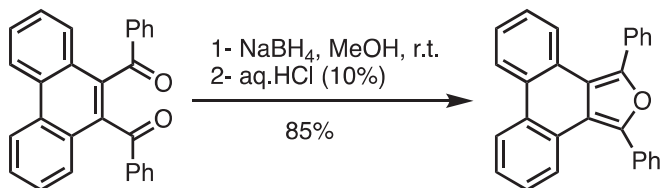
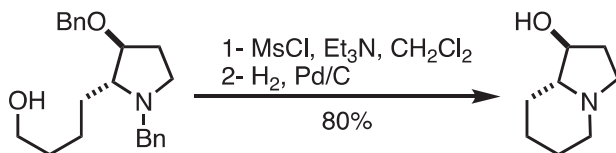


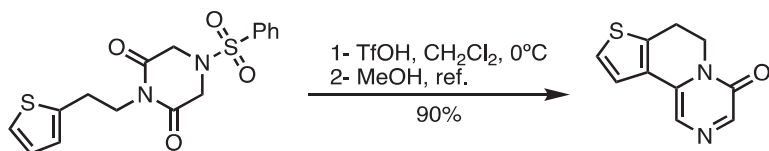
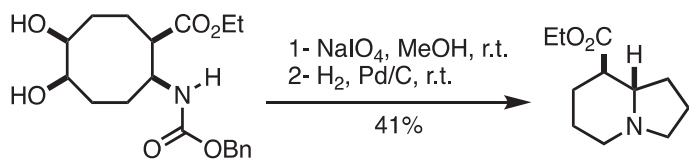
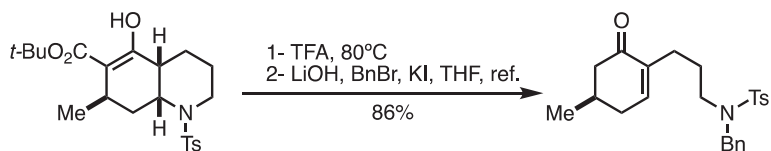
### Exercise 96

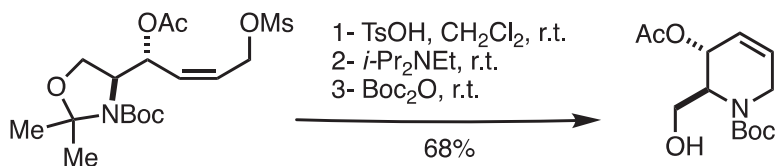
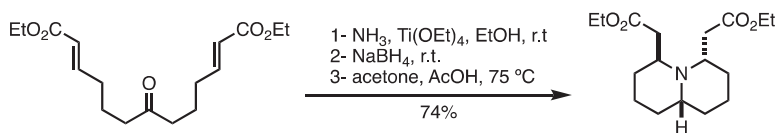
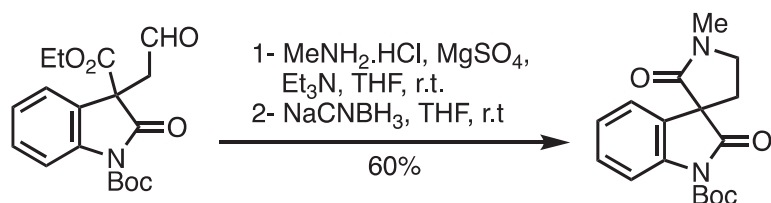


### Exercise 97

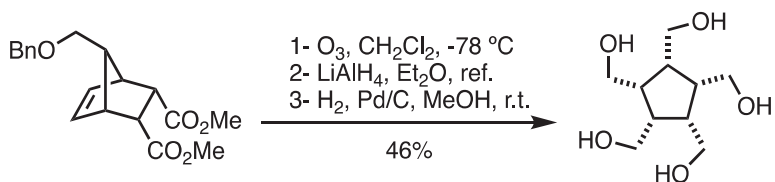
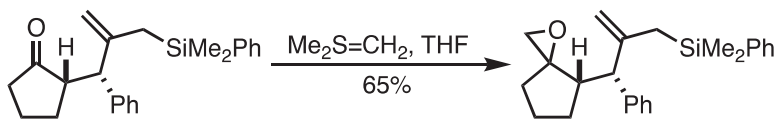
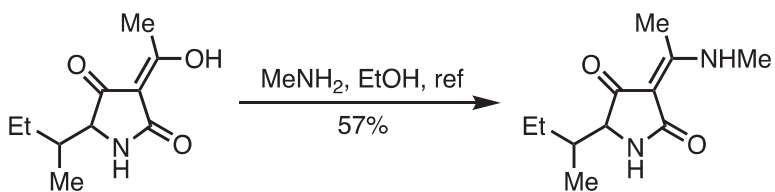


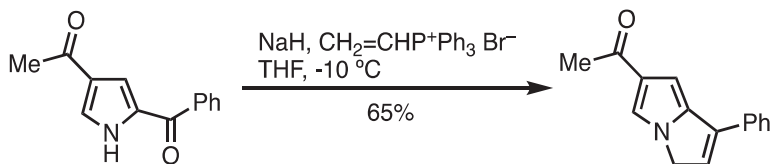
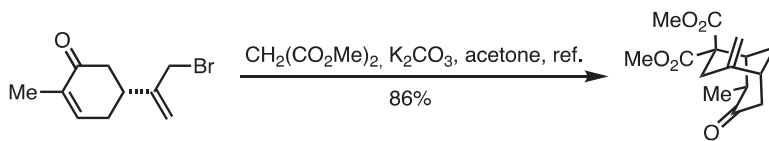
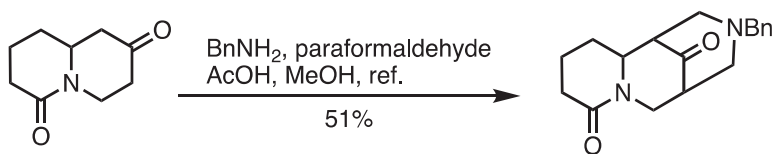
**Exercise 98****Exercise 99****Exercise 100**

**Exercise 101****Exercise 102****Exercise 103**

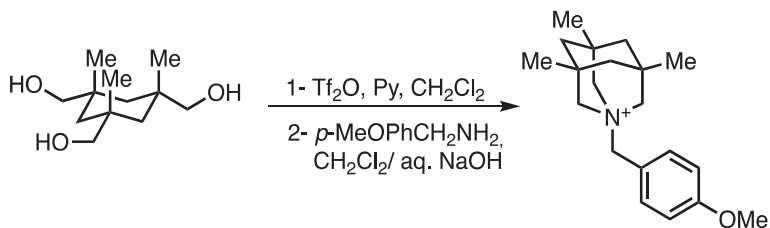
**Exercise 104****Exercise 105****Exercise 106**



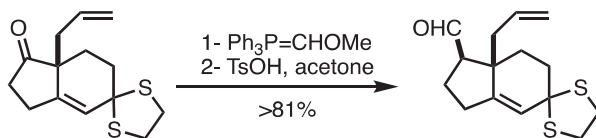
**Exercise 107****Exercise 108****Exercise 109**

**Exercise 110****Exercise 111****Exercise 112**

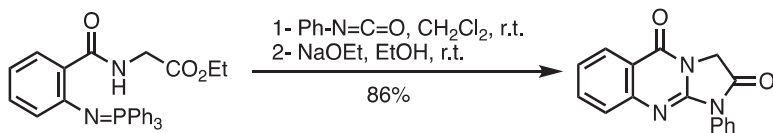
### Exercise 113



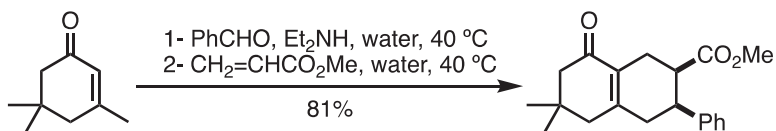
### Exercise 114



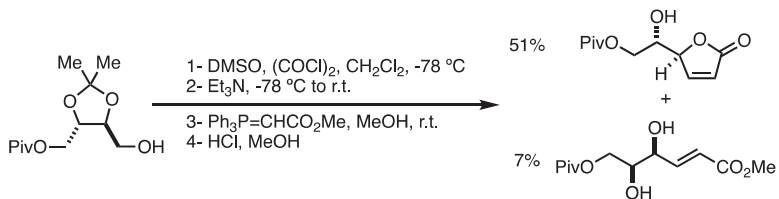
### Exercise 115



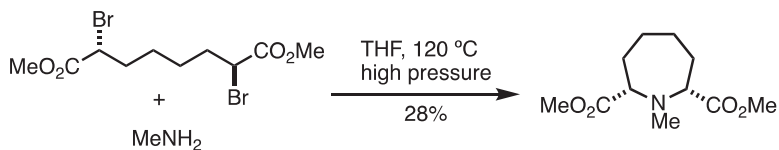
## Exercise 116

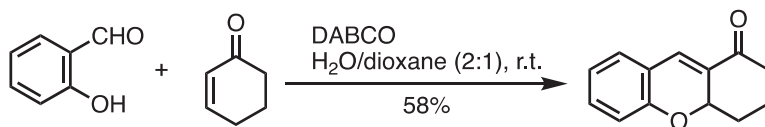
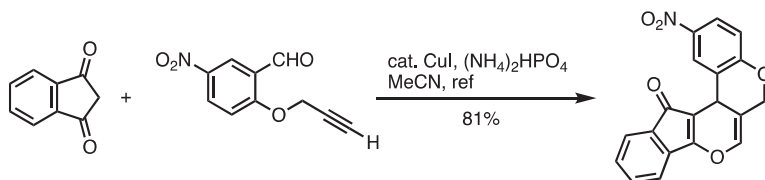
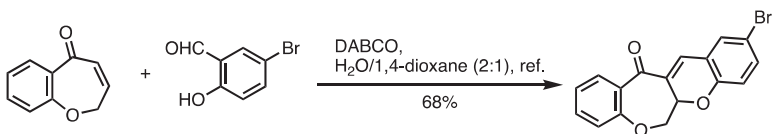


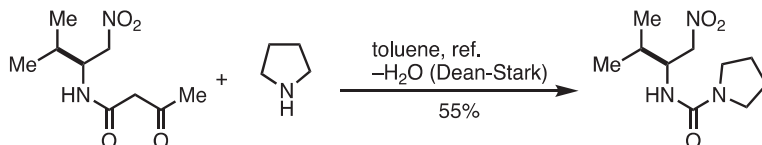
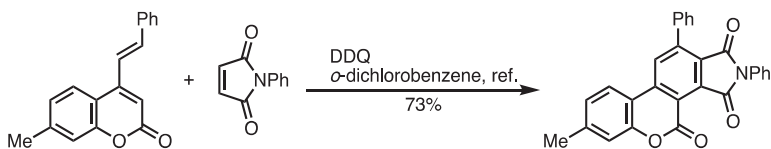
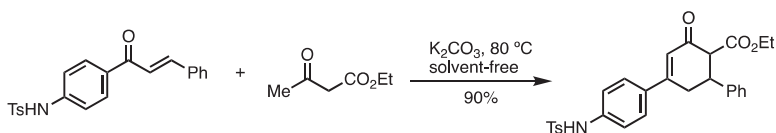
## Exercise 117



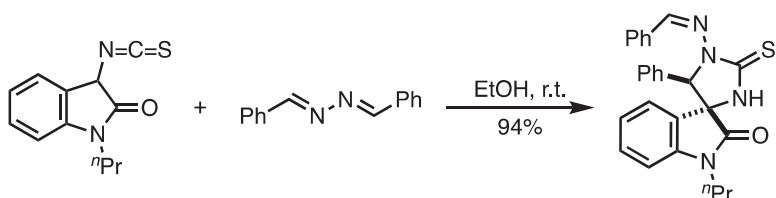
## Exercise 118



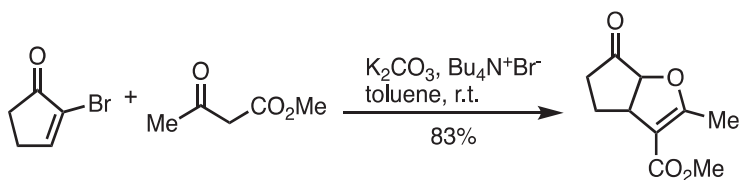
**Exercise 119****Exercise 120****Exercise 121**

**Exercise 122****Exercise 123****Exercise 124**

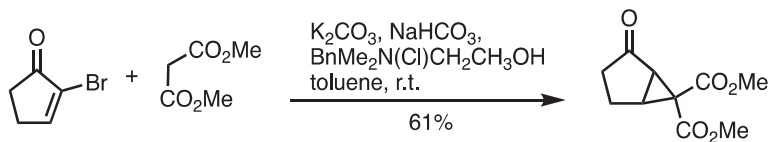
## Exercise 125

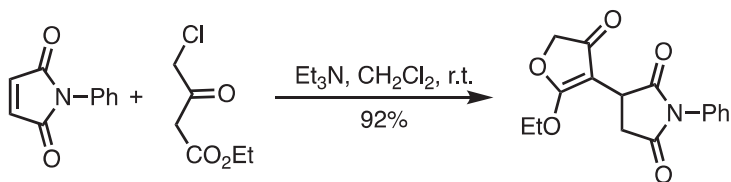
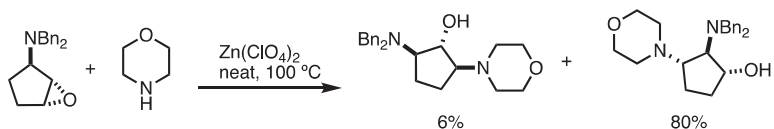
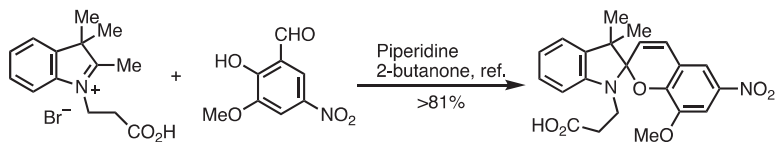


## Exercise 126



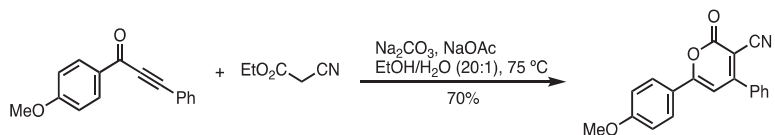
## Exercise 127



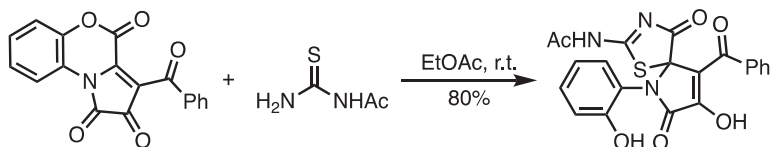
**Exercise 128****Exercise 129****Exercise 130**



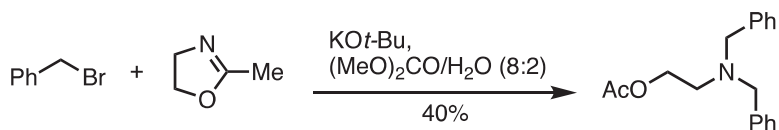
### Exercise 131

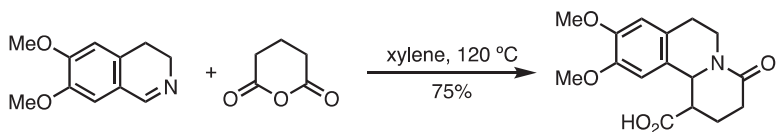
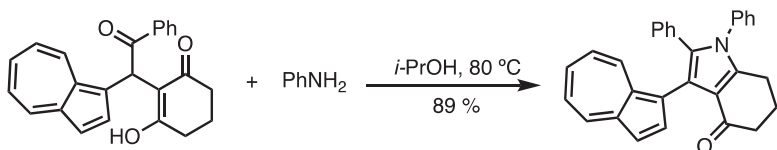
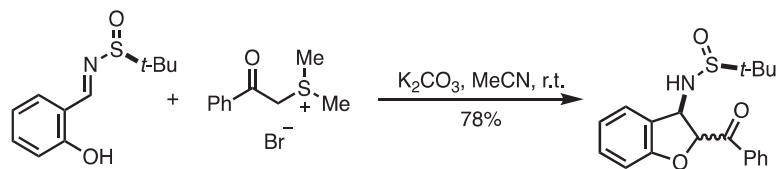


### Exercise 132

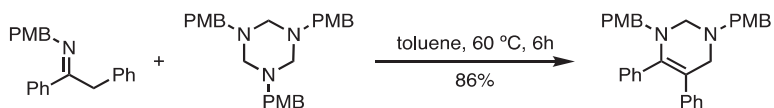


### Exercise 133

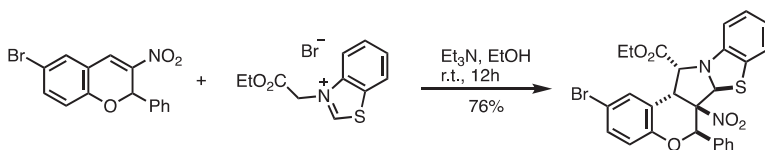


**Exercise 134****Exercise 135****Exercise 136**

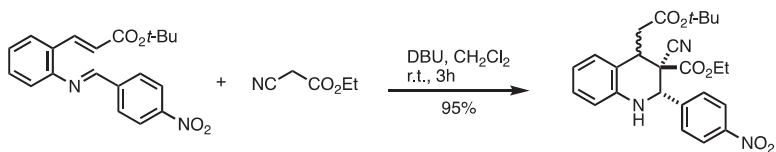
### Exercise 137

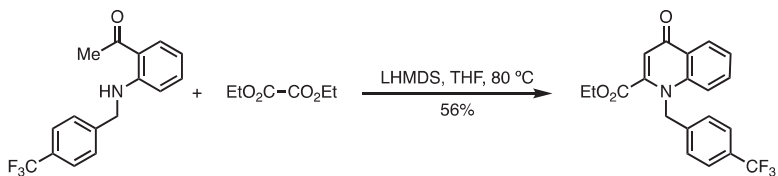
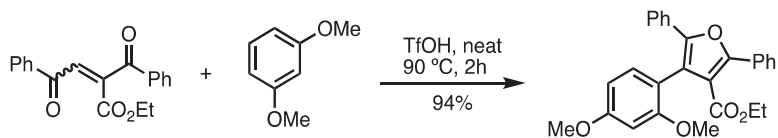
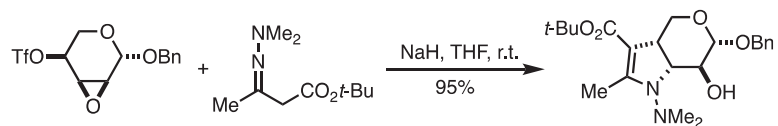


### Exercise 138

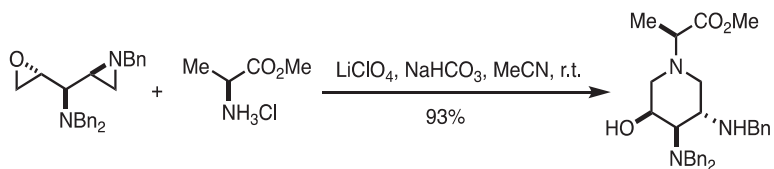


### Exercise 139

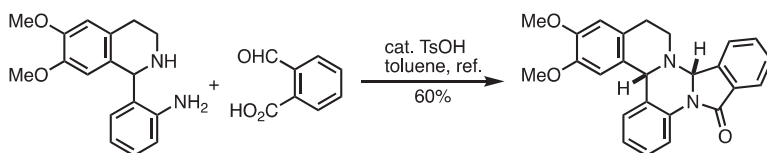


**Exercise 140****Exercise 141****Exercise 142**

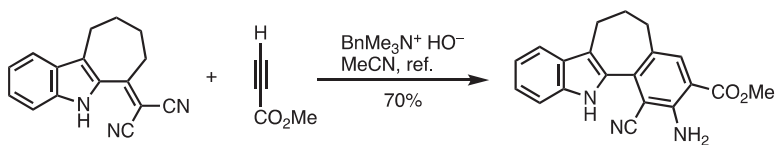
### Exercise 143

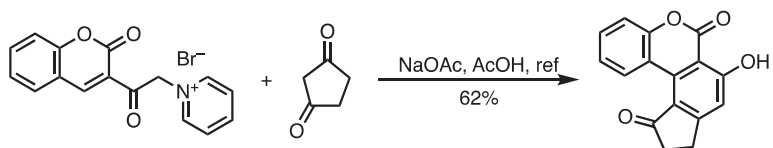
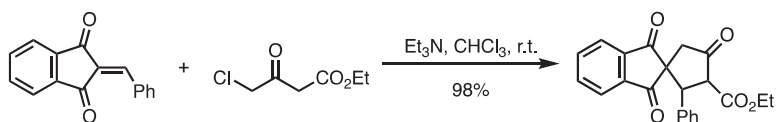
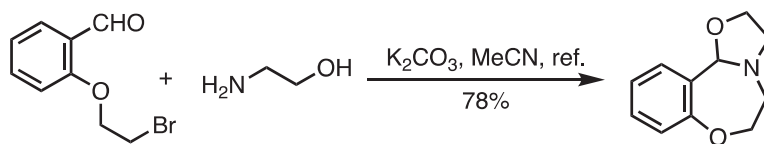


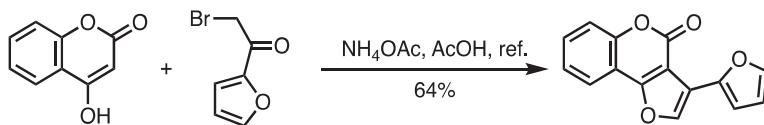
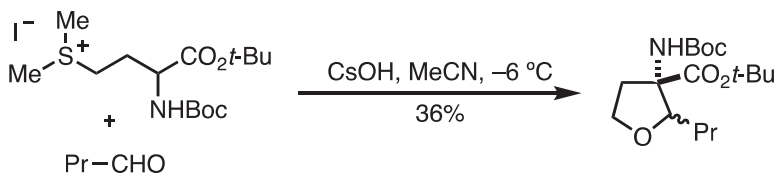
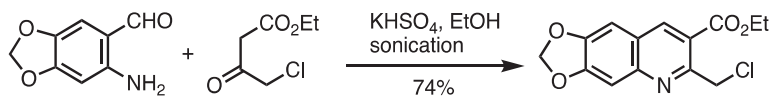
### Exercise 144

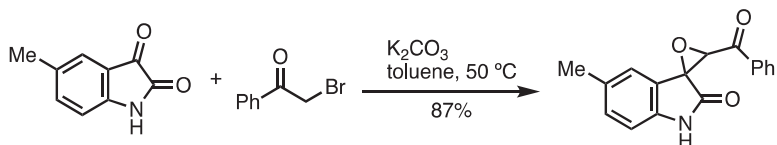
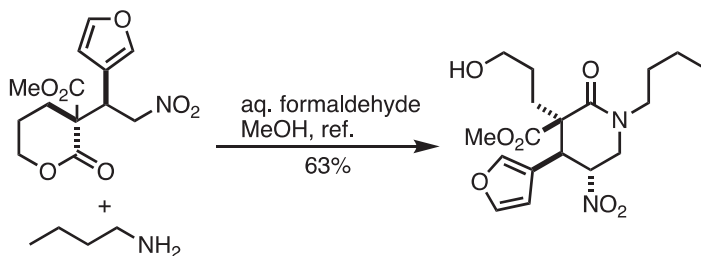
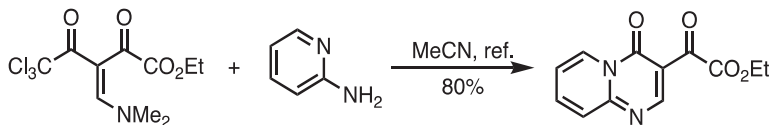


### Exercise 145

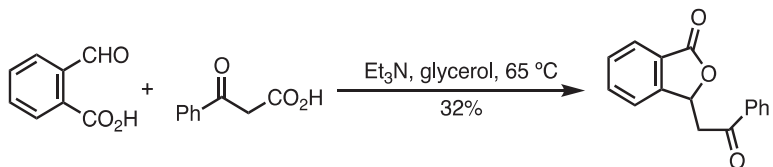
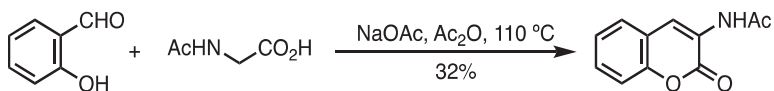
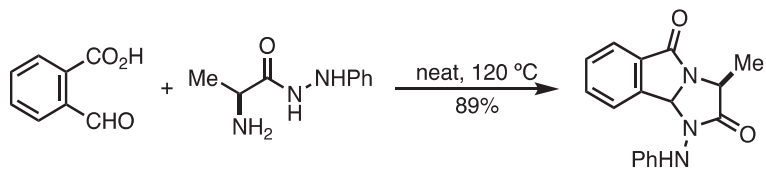


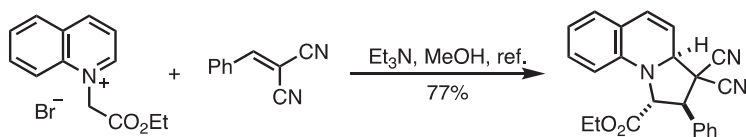
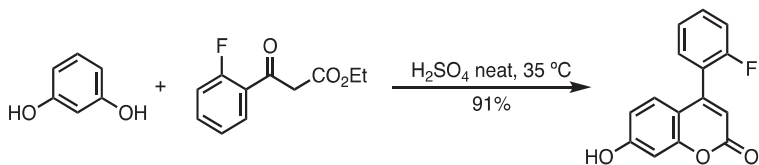
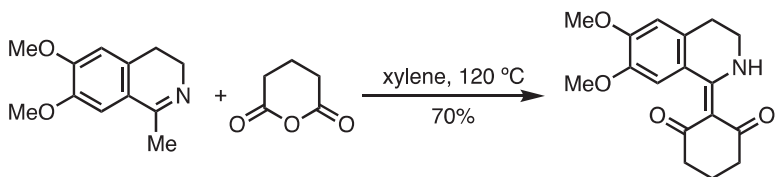
**Exercise 146****Exercise 147****Exercise 148**

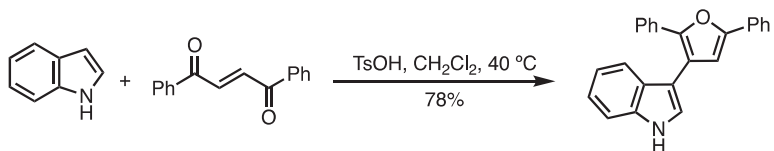
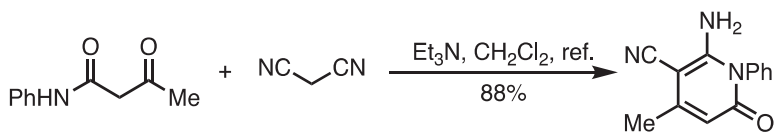
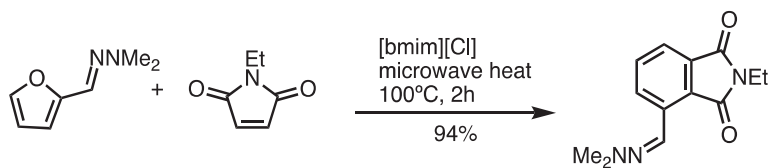
**Exercise 149****Exercise 150****Exercise 151**

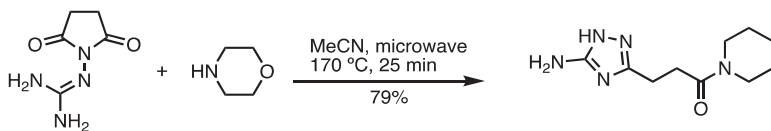
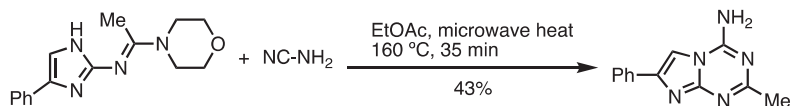
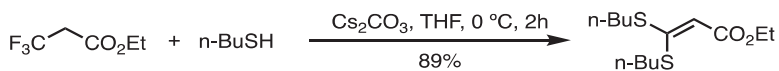
**Exercise 152****Exercise 153****Exercise 154**



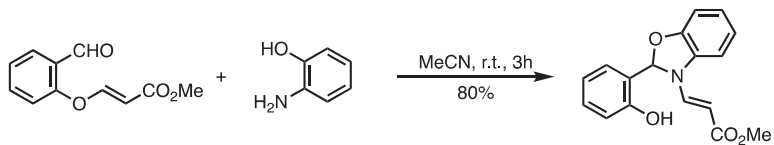
**Exercise 155****Exercise 156****Exercise 157**

**Exercise 158****Exercise 159****Exercise 160**

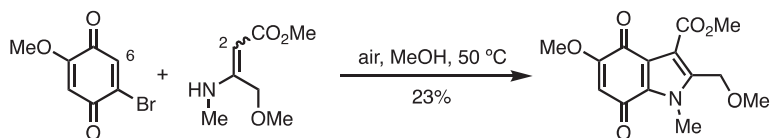
**Exercise 161****Exercise 162****Exercise 163**

**Exercise 164****Exercise 165****Exercise 166**

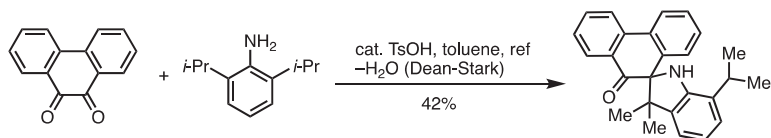
### Exercise 167



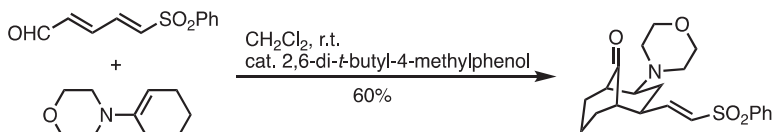
### Exercise 168



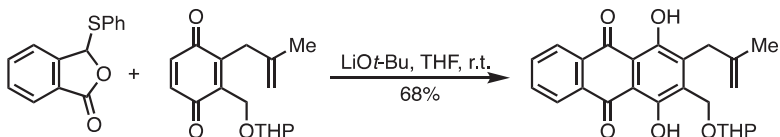
### Exercise 169



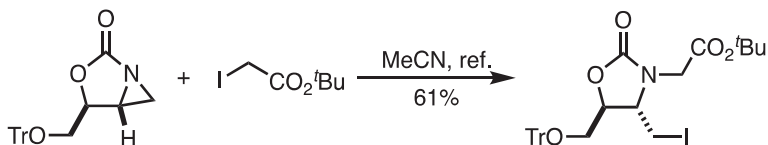
## Exercise 170

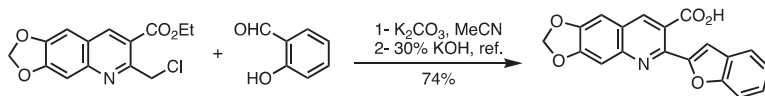
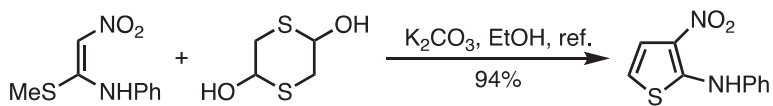
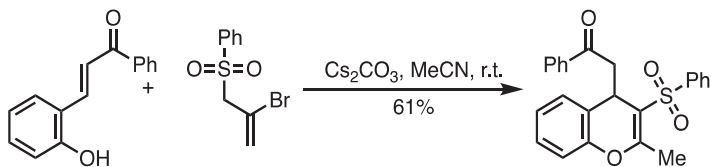


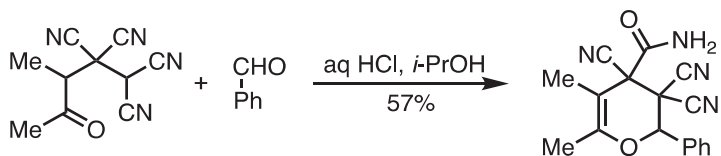
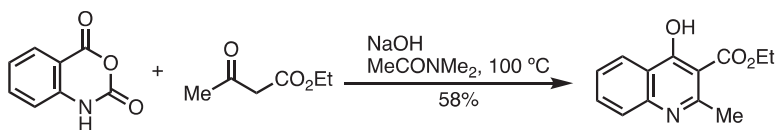
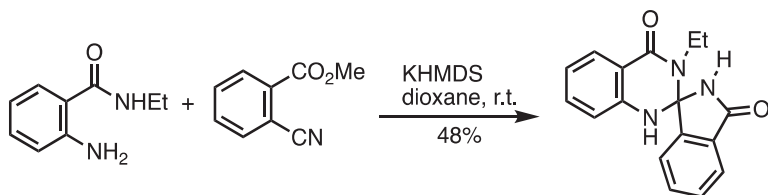
## Exercise 171



## Exercise 172

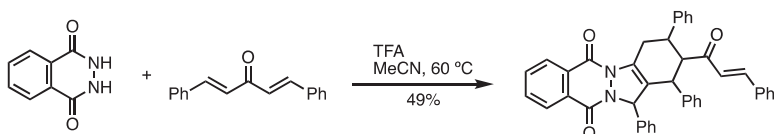


**Exercise 173****Exercise 174****Exercise 175**

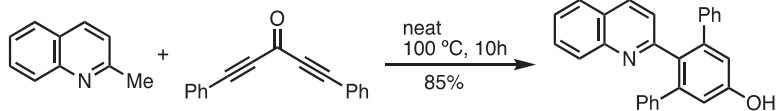
**Exercise 176****Exercise 177****Exercise 178**



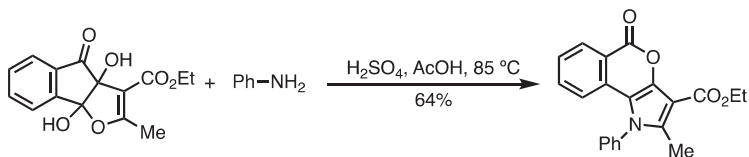
### Exercise 179

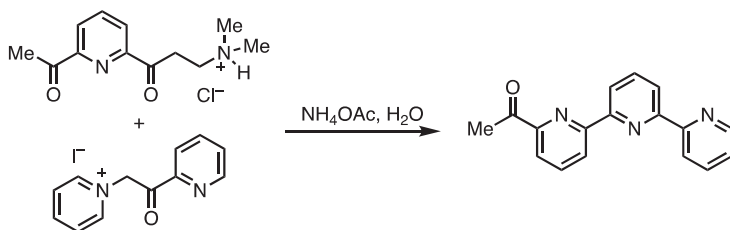
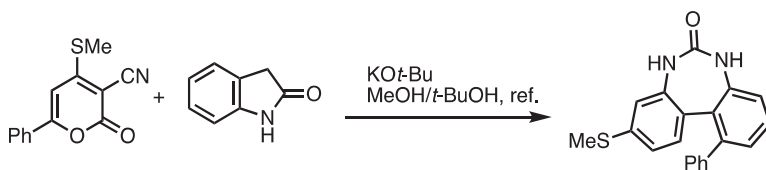
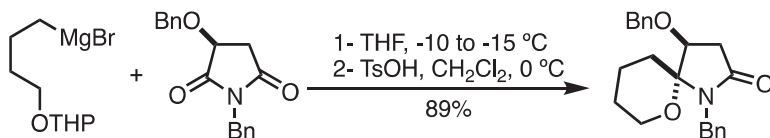


### Exercise 180

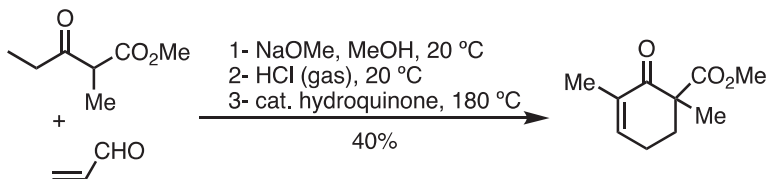


### Exercise 181

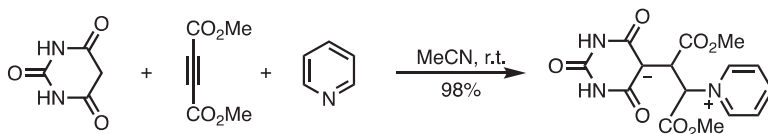


**Exercise 182****Exercise 183****Exercise 184**

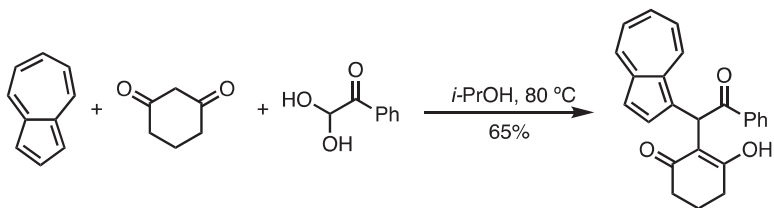
## Exercise 185

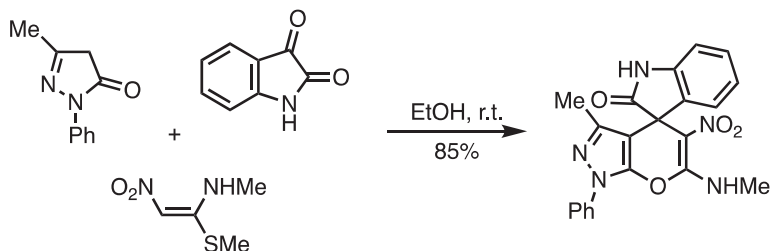
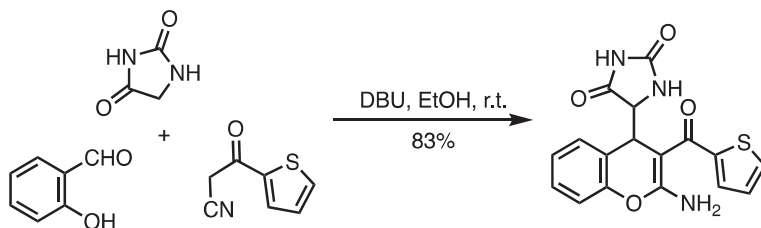
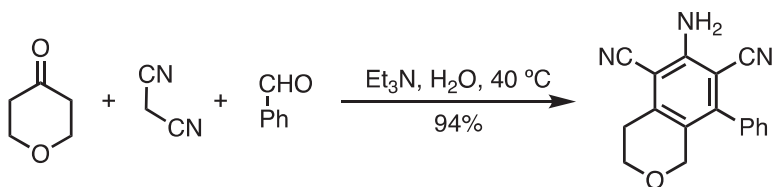


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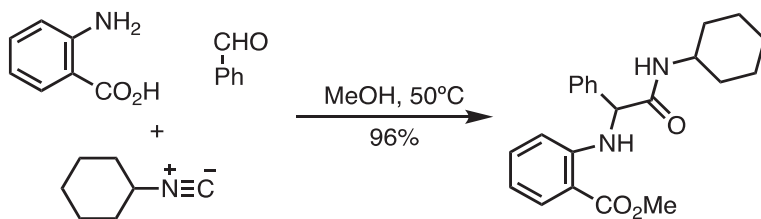


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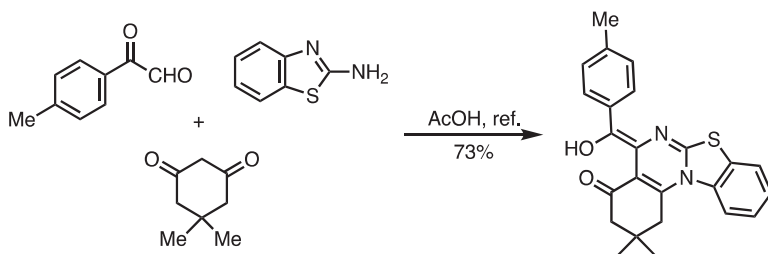


**Exercise 188****Exercise 189****Exercise 190**

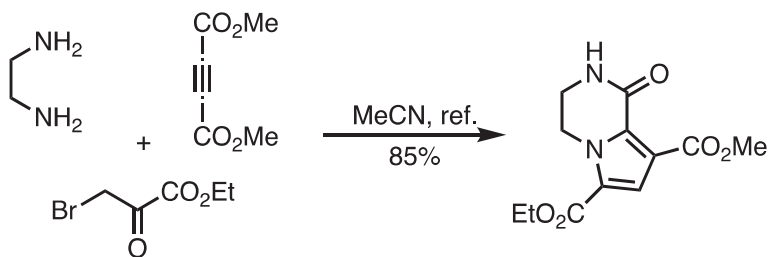
### Exercise 191

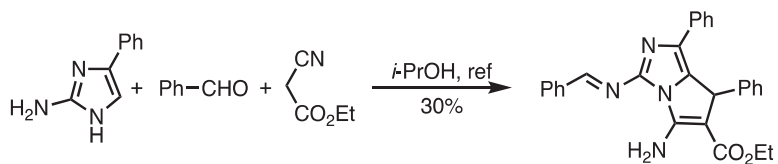
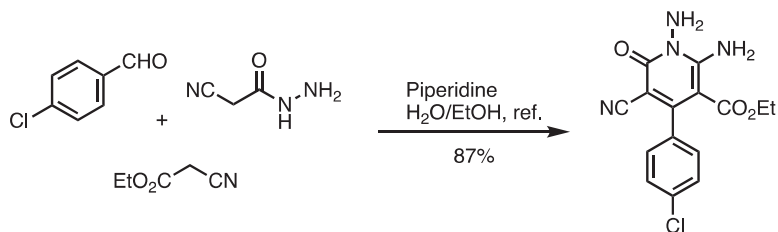
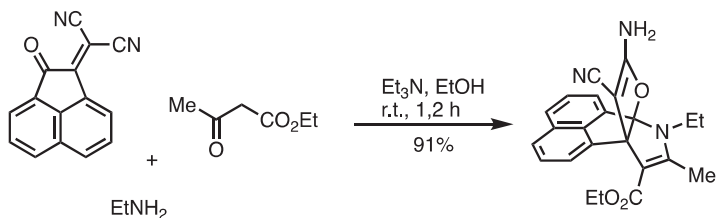


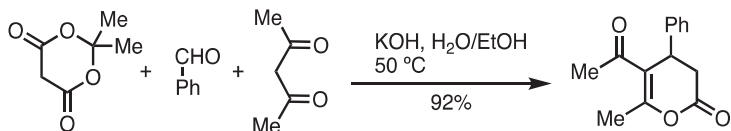
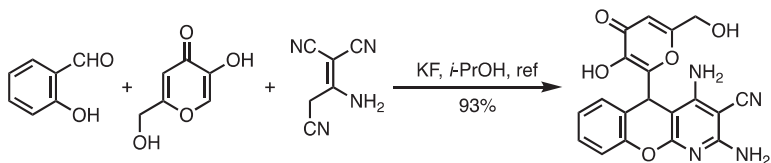
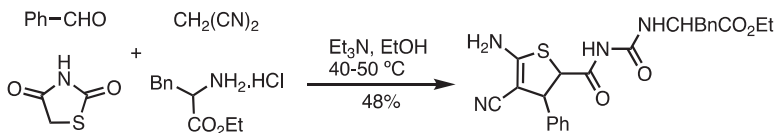
### Exercise 192

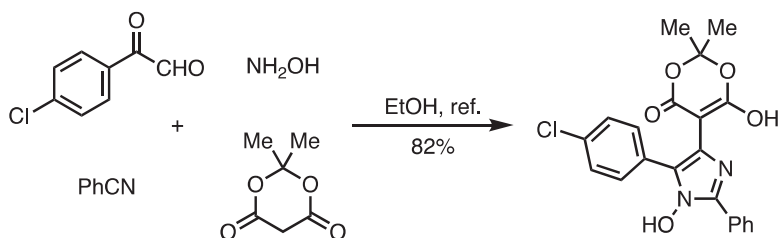


### Exercise 193



**Exercise 194****Exercise 195****Exercise 196**

**Exercise 197****Exercise 198****Exercise 199**

**Exercise 200**



# SOLUTIONS

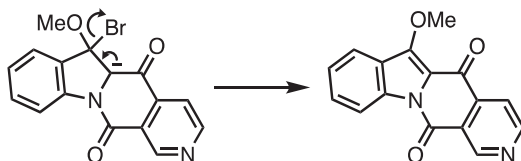
## Exercise 1

A lactone is formed by a  $S_N2$  reaction where the nucleophile is a carboxylate and the leaving-group an iodide.  $Ag^+$  is added to promote the nucleofugicity of iodine by complexation.

Zheng, Z.; and Bergmeier, S.C., *Arkivoc*, **3**, 40 (2019)

## Exercise 2

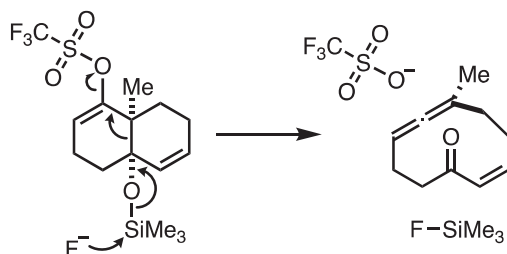
Of course, the mechanism does not consist in a direct displacement of bromine by methoxide in an  $S_N2$ -like reaction. This is not possible on an  $sp^2$  carbon. Rather, there is an addition-elimination mechanism in which methoxide adds to the olefin in the enone producing a carbanion stabilized by the ketone carbonyl that evolves by expelling bromide.



Davis, D.A.; Cory, M.; Fairley, T.A.; and Gribble, G.W.; *Arkivoc*, **3**, 53 (2019)

### Exercise 3

The fluoride anion in TBAF attacks the silicon atom in the silyl ether thanks to the high affinity of fluorine for silicon. This promotes an electron movement that causes a ring fragmentation and the formation of an allene while the charge ends up in a very stable triflate anion.



This electron movement demands a precise alignment of the orbitals involved.

Xu, D.; Drahl, M.A.; and Williams, L.J., *Beilstein J.Org.Chem.* **7**, 937 (2011)

### Exercise 4

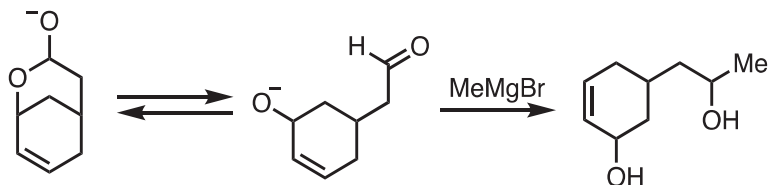
Tosylation of the alcohol is followed by intramolecular displacement of the resulting tosylate by attack of the deprotonated nitrogen atom in the carbamate.



Garad, D.N.; Tanpure, S.D.; and Mhaske, S.B., *Beilstein J.Org.Chem.* **11**, 1008 (2015)

### Exercise 5

One molecule of Grignard reagent deprotonates the hydroxy group of the hemiacetal. A second molecule of the Grignard reagent adds to the aldehyde in equilibrium with the deprotonated hemiacetal.



Roy, J.; Mal, T.; Jana, S.; and Mal, D., *Beilstein J.Org.Chem.* **12**, 531 (2016)

### Exercise 6

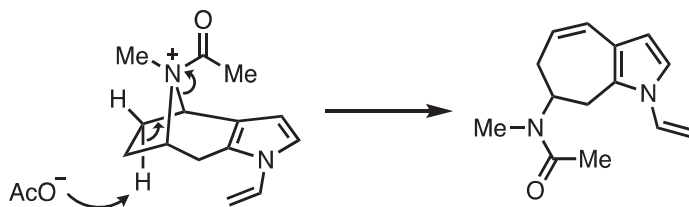
There is a base-induced double elimination of HBr promoted by a strong hindered base that produces a highly strained cyclic alkyne.

Li, Xu; Liu, Z.; and Dong, S., *RSC Adv.* **7**, 44470 (2017)

### Exercise 7

1– Acetylation of the aliphatic amine by acetic anhydride leads to an acetyl ammonium salt and the acetate anion.

2– An olefin is formed by elimination —assisted by the acetate anion— of the positive nitrogen of the acetyl ammonium salt. This nitrogen is a good leaving group because it departs easily as a stable amide.

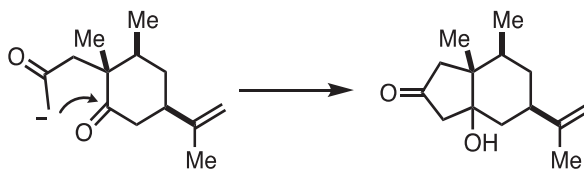


Varlamov, A.V.; Borisova, T.N.; Voskressensky, L.G.; Brook, A.A.; and Chernyshev, A.I., *Arkivoc*, **2**, 147 (2000).

## Exercise 8

This is an intramolecular aldol condensation.

1– The KOH is able to form anions by abstraction of any of the acidic hydrogens at the  $\alpha$  position of both ketones, but only the anion formed on the methyl ketone has a favorable evolution by forming a stable five-membered ring by attack on the cyclohexanone.



2– The resulting  $\beta$ -hydroxyketone suffers dehydration via an  $E_{1cB}$  mechanism.

Srikrishna, A.; and Reddy, T.J., *Arkivoc*, **8**, 9 (2001)

## Exercise 9

1– The catalytic hydrogenation reduces the olefin and removes the benzyl protecting groups

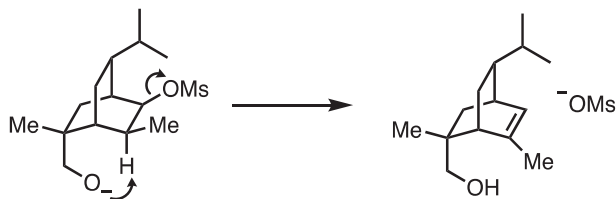
2– *p*-Toluenesulfonic acid catalyzes the cyclization of the dihydroxyacid to a stable five-membered lactone.

Chandrasekhar, M; Chandra, K.L.; and Singh, V.K., *Arkivoc*, **7**, 34 (2002)

## Exercise 10

1– Lithium aluminium hydride reduces the ester to an alcohol that is formed as an aluminium alkoxide.

2– The alkoxide promotes an E<sub>2</sub> elimination of mesylate by intramolecular attack on a hydrogen via a favorable six-membered structure. This undesired elimination can be prevented by performing the reduction under milder conditions at room temperature.



Lakshmi, R.; and Gharpure, S.J., *Arkivoc*, **7**, 52 (2002)

## Exercise 11

1– Protonation of the hydroxy group in the hemiacetal leads to detachment of water and formation of a cation stabilized by a neighbouring oxygen.

2– This cation is intramolecularly trapped by the secondary alcohol in the molecule.

Lakshmi, R.; and Balasubramanian, K.K., *Arkivoc*, **3**, 140 (2003)

## Exercise 12

1– Sodium methoxyde attacks the carbonyl from the acetate, giving rise to methyl acetate and an alkoxide.

2– The alkoxide displaces intramolecularly the chlorine atom via a S<sub>N</sub>2 reaction leading to the epoxide.

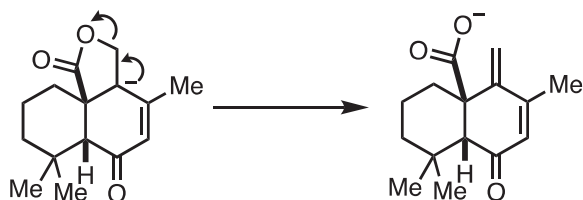
Boyd, D.R.; Sharma, N.D.; Kerley, N.A.; McConville, G.; Allen, C.C.R.; and Blacker, A.J., *Arkivoc*, **7**, 32 (2003)

### Exercise 13

Elimination occurs during the attempted basic hydrolysis of a lactone.

1– The hydroxide anion abstracts a proton on  $\gamma$  to the unsaturated ketone, forming an anion stabilized by extended resonance.

2– This anion evolves by expulsion of the carboxylate of the lactone.



In another experiment, it was determined that hydrogenation of the alkene in the starting compound prevents the elimination as it disrupts the stabilization of the intermediate anion by extended delocalization.

Watanabe, H.; Yamaguchi, T.; Furuuchi, T.; Kido, M.; Bando, M.; and Kitahara, T., *Arkivoc*, **8**, 267 (2003)

### Exercise 14

1– Hydrogenation under Lindlar's catalyst transforms the alkyne into a (*cis*)-alkene.

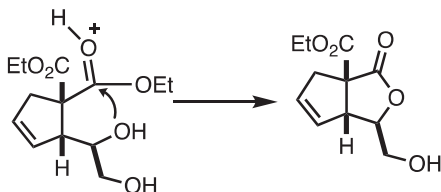
2– A cyclic hemiacetal is formed by attack of the secondary alcohol on the ketone.



Chandrasekhar, S.; Narsihmulu, C.; Jagadeshwar, V.; and Shameem sultana, S., *Arkivoc*, **3**, 92 (2005)

### Exercise 15

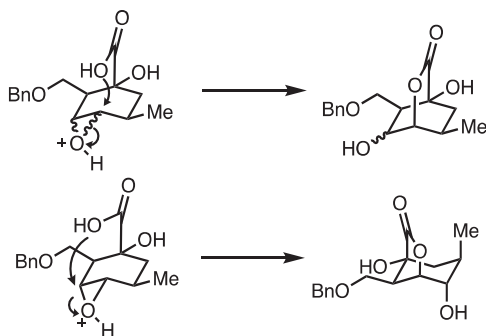
- 1– The acidic conditions deprotect the diol.
- 2– The secondary alcohol attacks one of the esters forming a lactone.



Sinha, S.; Bhaumik, T.; and Ghosh, S., *Arkivoc*, **11**, 24 (2005)

### Exercise 16

- 1– *m*-Chloroperbenzoic acid epoxidizes the alkene.
- 2– The acid opens the epoxide previously activated by protonation under acidic conditions. Depending on the carbon atom of the epoxide being attacked by the acid by a  $S_N2$  reaction, either product is obtained. Either epimer on C-6 of the product on the left is obtained depending on the epoxide being formed on the first step.



Note: epoxidations with *m*-chloroperbenzoic acid occur under acidic conditions because the corresponding acid contaminates the commercial peracid. Furthermore, the corresponding acid is generated *in situ* as the peracid oxidizes the alkene. To avoid acid-catalysed reactions, a buffer or a base can be added.

Helliwell, M.; Thomas, E.J.; and Vickers, C., *Arkivoc*, **7**, 209 (2007)

## Exercise 17

1– Osmium tetroxide produces the dihydroxylation of the alkene. The very expensive and toxic  $\text{OsO}_4$  is used in catalytic amounts, and *N*-methylmorpholine *N*-oxide in excess reoxidizes the reduced osmium to  $\text{OsO}_4$ .

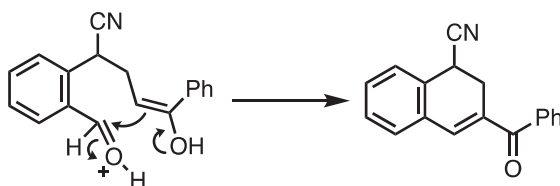
2– A  $\gamma$ -lactone is formed by condensation of one of the secondary alcohols with the carboxylic acid.

Chouthaiwale, P.V.; Kotkar, S.P.; and Sudalai, A, *Arkivoc*, **2**, 88 (2009)

## Exercise 18

1– The ethylidene acetal is hydrolysed to aldehyde.

2– There is an intramolecular aldol condensation between the aldehyde and the ketone.

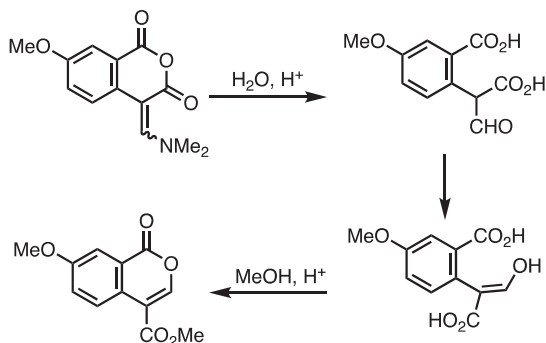


Panasiewicz, M.; Zdrojewski, T.; Chrulski, K.; Wojtasiewicz, A.; and Jończyk, A., *Arkivoc*, **7**, 98 (2009)



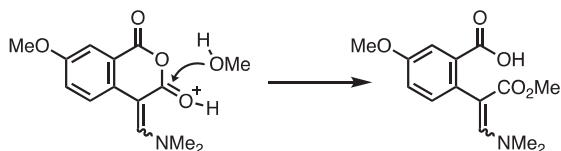
## Exercise 19

In line with a naïve vision, the anhydride would be hydrolysed to a diacid and the enamine to an aldehyde. Then the enol tautomer of the aldehyde would condense with one of the acids, while the other acid would be transformed into a methyl ester. This route is not possible because there is no water to make a hydrolysis.

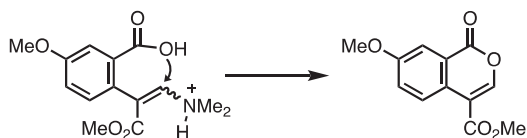


A more plausible alternative would be the following:

1– After protonation of the anhydride, one of the carbonyl groups is attacked by methanol resulting in the formation of a methyl ester and release of a carboxylic acid.



2– Nitrogen is transformed into a good-leaving group by protonation. This allows a conjugated attack of the carboxylic acid on the alkene with release of dimethylamine via an addition-elimination mechanism.

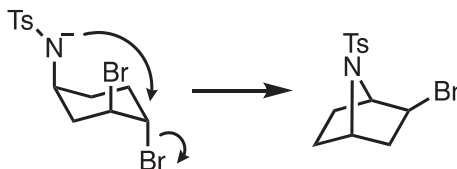


Delioeroğlu, M.K.; Özcan, S.; and Balci, M., *Arkivoc*, **2**, 148 (2010)

## Exercise 20

1– Sodium hydride abstracts the acidic proton of the sulfonamide producing the anion  $R-N^-Ts$  while  $H_2$  is released.

2– This anion displaces intramolecularly the distal bromide via a  $S_N2$  reaction. Observe that this  $S_N2$  substitution with inversion of configuration is possible thanks to the propitious stereochemistry of the bromine involved.



Marco-Contelles, J.; Gómez-Sánchez, E.; Samadi, A.; Soriano, E.; Valderas, C.; Álvarez-Pérez, M.; and Carreiras, M., *Arkivoc*, **3**, 56 (2010)

## Exercise 21

1– The catalytic hydrogenation removes the Cbz protecting group.

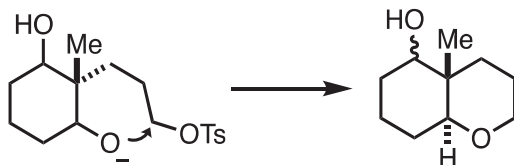
2– The amine condenses with one of the ketones with formation of an enamine stabilized by conjugation with the remaining ketone.

Miao, L.; Shu, H.; Noble, A.R.; Fournet, S.P.; Stevens, E.D.; and Trudell, M.L., *Arkivoc*, **4**, 6 (2010)

## Exercise 22

1– The first step is a selective tosylation of the less hindered primary alcohol.

2– Under the basic conditions, one of the secondary alcohols is converted in an alkoxide that displaces the sulfonate yielding a cyclic ether.

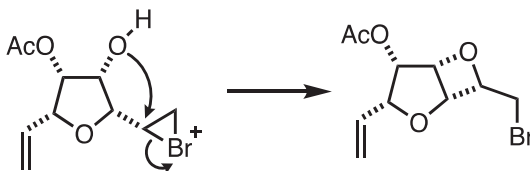


Basu, D.; Chandrasekharam, M.; Mainkar, P.S.; and Chandrasekhar, S., *Arkivoc*, **2**, 355 (2011)

## Exercise 23

1– One of the olefins reacts with *N*-bromosuccinimide yielding a three-membered bromonium ion.

2– The positively charged bromine atom is displaced by the neighbouring alcohol via a  $S_N2$  substitution. It is remarkable that a tense four-membered ring is formed rather than a more stable five-membered one.



Aljarilla, A.; and Plumet, J., *Arkivoc*, **3**, 20 (2011)

## Exercise 24

Of course the mechanism has no resemblance whatsoever to the bromination of aromatic compounds.

1– Bromine adds to the olefine giving rise to a 1,2-dibromocompound. The mechanism is the one operating in normal olefines, with a twist: the intermediate bromonium ion evolves by breakage of the three-membered ring and formation of an oxonium cation that is trapped by bromide. Thus, the addition is not necessarily *anti*.

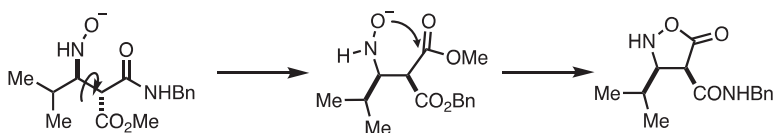
2– Triethylamine produces the elimination of HBr.

Gómez, A.M.; Pedregosa, A.; Valverde, S.; and López, J.C., *Arkivoc*, **3**, 33 (2011)

## Exercise 25

1– The fluoride ion in TBFA deprotects the TMS group in the hydroxylamine.

2– The hydroxy group displaces the methoxy group in the ester.



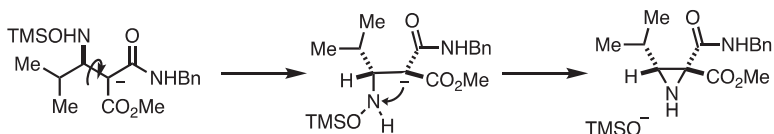
Tolomelli, A.; Cardillo, G.; Gentilucci, L.; Juris, R.; Viola A.; and Juaristi, E., *Arkivoc*, **5**, 196 (2012)

## Exercise 26

This is an interesting case in which a silyloxyde works as a leaving-group while a nitrogen atom operates as an electrophile.

1– Potassium *t*-butoxyde abstracts the acidic proton located between both carbonyl groups.

2– The resulting anion displaces intramolecularly the trimethylsilyloxy group resulting in cyclization to an aziridine.

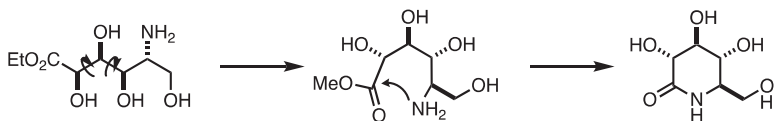


Tolomelli, A.; Cardillo, G.; Gentilucci, L.; Juris, R.; Viola A.; and Juaristi, E., *Arkivoc*, **5**, 196 (2012)

## Exercise 27

1– The catalytic hydrogenation reduces the azide to amine and removes the benzyl protecting groups.

2– The amine condenses with the ester yielding a lactam.

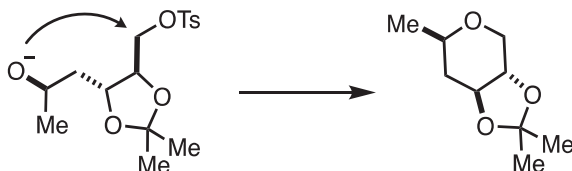


Ravinder, M.; Reddy, T.N.; Mahendar, B.; and Rao, V.J., *Arkivoc*, **9**, 287 (2012)

### Exercise 28

1– The fluoride anion in TBAF attacks the silicon in the silyl ether liberating an alkoxide.

2– The alkoxide reacts intramolecularly with the tosylate.

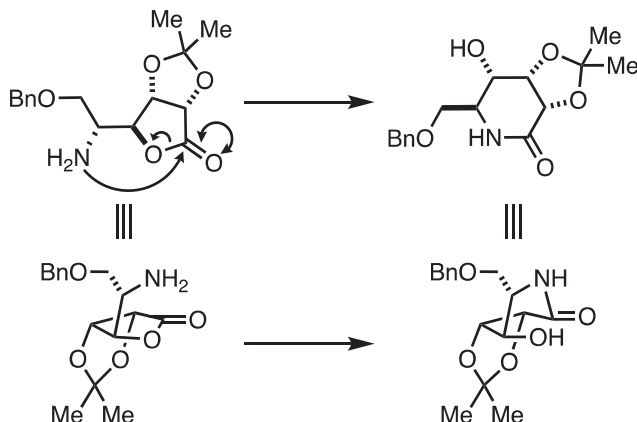


Akkala, B.; and Damera, K., *Arkivoc*, **4**, 164 (2013)

### Exercise 29

1– Trifluoroacetic acid causes the removal of the Boc protecting group.

2– The resulting amine attacks the carbonyl of the lactone and expels an alcohol.

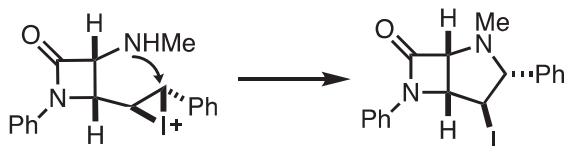


Chavan, S.P.; Dumare, N.B.; Pawar, K.P.; Chavan, P.N.; and Khairnar, L., *Arkivoc*, **2**, 137 (2016)

### Exercise 30

1- Iodine reacts with the olefin resulting in the formation of iodonium cation inside a three-membered ring.

2- The iodine is displaced intramolecularly by attack of the amine.

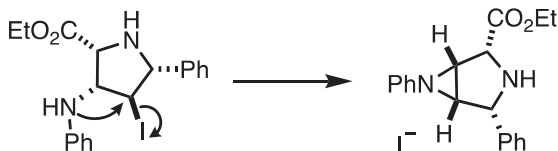


Kumar, Y.; Kulia, B.; Singh, P.; and Bhargava, G., *Arkivoc*, 6, 23 (2016)

### Exercise 31

1- Sodium ethoxide breaks the lactam bond releasing an ethyl ester and an amine. Normally amides demand very harsh conditions for hydrolysis or alcoholysis. This amide can be cleaved under relatively mild conditions because: a) it leads to the release of tension in a strained four-membered ring; b) nitrogen on the  $\alpha$  position increases the reactivity of the lactam carbonyl via inductive effect.

2- The resulting amine displaces the iodine forming an aziridine ring.

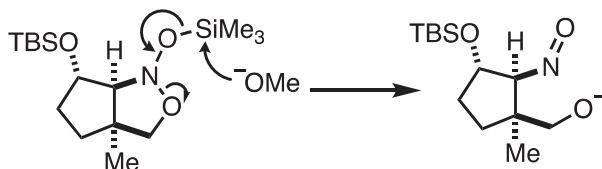


3- Adventitious water hydrolyses the ethyl ester.

Kumar, Y.; Kulia, B.; Singh, P.; and Bhargava, G., *Arkivoc*, 6, 23 (2016)

### Exercise 32

1– Methoxide attacks the silicon in the TMS ether resulting in the formation of an N=O bond and delivery of an alkoxide.



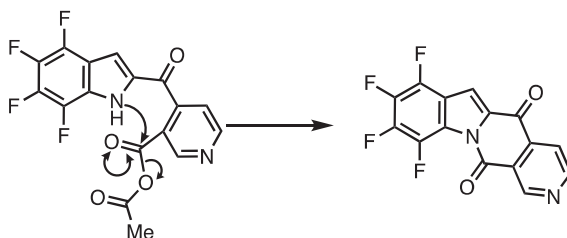
2– Tautomerization of the nitroso compound to oxime and protonation of the alkoxide yield the final compound.

Lozanova, A.V.; Stepanov, A.V.; Zlokazov, M.V.; and Veselovsky, V.V., *Arkivoc*, **3**, 217 (2017)

### Exercise 33

1– Acetic anhydride reacts with the acid forming a mixed anhydride.

2– The nitrogen of the indole attacks the mixed anhydride displacing an acetate.



Gruver, E.J.; Onyango, E.O.; and Gribble, G.W., *Arkivoc*, **3**, 144 (2018)

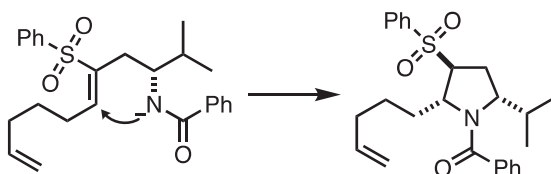


### Exercise 34

The mechanism does not consist in an  $S_N2$  reaction with an anion on the nitrogen displacing an acetate. Rather, a more elaborate mechanism occurs with the intermediation of an unsaturated sulfone.

1– The base abstracts a proton resulting in a carbanion stabilized by the sulfone. This anion evolves inducing the elimination of acetate and formation of an olefin.

2– An anion formed on the nitrogen attacks the olefin activated by conjugation with the sulfone.



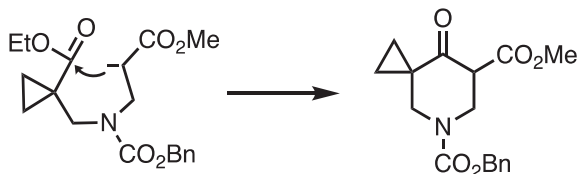
Berry, M.B.; Craig, D.; Jones, P.S.; and Rowlands, G.J., *Beilstein J.Org.Chem.* **3**, No 39 (2007)

### Exercise 35

This is an example of the so-called Dickmann cyclization.

1– Sodium hydride abstracts a proton on  $\alpha$  to the carbonyl of the ester on the right, resulting in the formation of a carbanion and evolution of  $H_2$ .

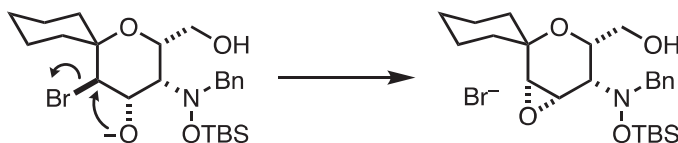
2– This carbanion attacks the other ester with expulsion of ethoxide.



Kodimuthali, A.; Prasunamba, P.L.; and Pal, M., *Beilstein J.Org.Chem.* **6**, No 71 (2010)

**Exercise 36**

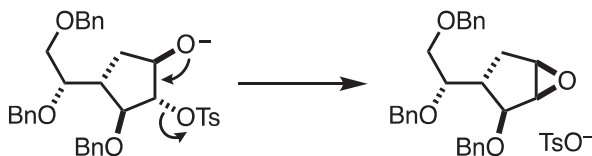
- 1– Sodium borohydride reduces the ketone to an alcohol.
- 2– The alcohol displaces the bromine intramolecularly yielding an epoxide.



Pfrenge, F.; and Reissig, H.-U., *Beilstein J.Org.Chem.* **6**, No 75 (2010)

**Exercise 37**

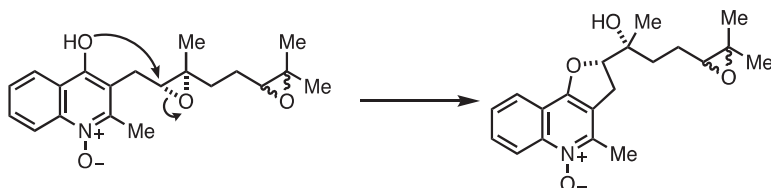
- 1– The methoxide anion attacks the benzoate resulting in the formation of methyl benzoate and an alkoxide.
- 2– The alkoxide displaces intramolecularly the tosylate yielding an epoxide.



Frigell, J.; and Cumpstey, I., *Beilstein J.Org.Chem.* **6**, 1127 (2010)

### Exercise 38

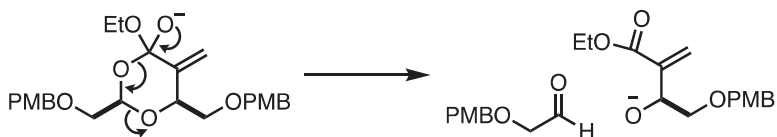
- 1- Catalytic hydrogenation causes debenzoylation of the phenol.
- 2- The phenol attacks the proximal epoxide producing a five-membered ring and an alcohol.



Li, X.-W.; Herrmann, J.; Zang, Y.; Grellier, P.; Prado, S.; Müller, R.; and Nay, B., *Beilstein J.Org.Chem.* **9**, 1551 (2013)

### Exercise 39

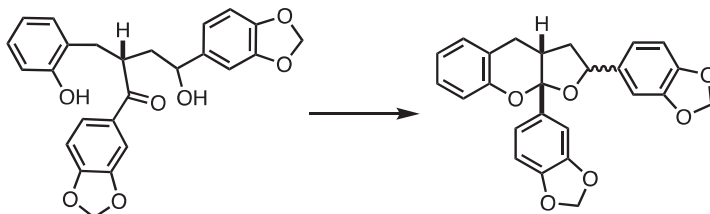
- 1- Reaction of triethylamine with ethanol generates ethoxide that attacks the carbonyl in the ester.
- 2- The resulting tetrahedral intermediate evolves with the generation of an ethyl ester, PMBO-CH<sub>2</sub>-CHO and an alkoxide that gives the final product by protonation.



Ilangovan, A.; and Saravanakumar, S., *Beilstein J.Org.Chem.* **10**, 127 (2014)

**Exercise 40**

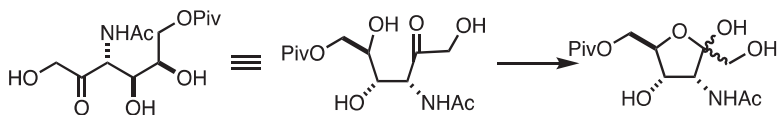
- 1– The dioxolane is hydrolysed to ketone.
- 2– The phenol and the alcohol react with the ketone to form an acetal.



Paterson, D.L.; and Barker, D., *Beilstein J.Org.Chem.* **11**, 265 (2015)

**Exercise 41**

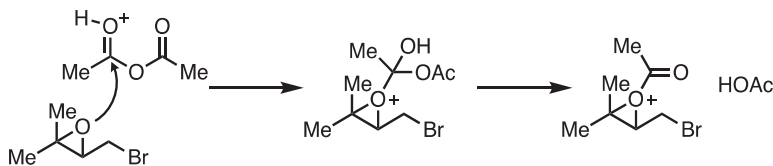
- 1– The acidic conditions cause the hydrolysis of the acetal and the trityl protecting group.
- 2– One of the hydroxy groups attacks the ketone forming a cyclic hemiacetal.



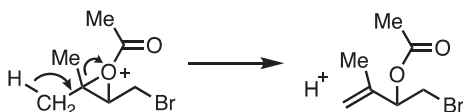
Bella, M.; Kooš, M.; and Lin, C.-H., *Beilstein J.Org.Chem.* **11**, 1547 (2015)

### Exercise 42

1– The oxygen of the epoxide attacks acetic anhydride activated by protonation expelling acetic acid.



2– The positively charged oxygen operates as a good-leaving group as the three-membered ring is opened and an olefin is formed.

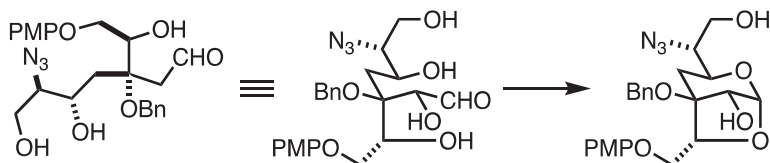


Bew, S.P.; Hiatt-Gipson, G.D.; Mills, G.P.; and Reeves, C.E., *Beilstein J.Org.Chem.* **12**, 1081 (2016)

### Exercise 43

1– Under the acidic conditions, the isopropylidene acetal is hydrolysed and the resulting cyclic hemiacetal equilibrates with the open form containing an aldehyde.

2– The aldehyde reacts with two of the alcohols to form an acetal inside a bicyclic system.



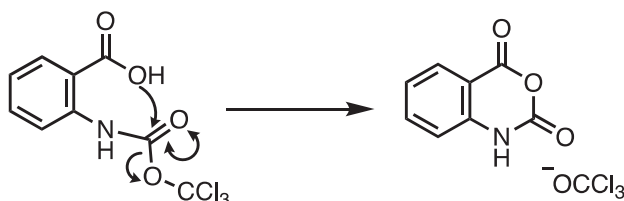
Markad, P.R.; Kumbhar, N.; and Dhavale, D.D., *Beilstein J.Org.Chem.* **12**, 1765 (2016)

## Exercise 44

The reagent  $(\text{Cl}_3\text{CO})_2\text{CO}$  —normally called triphosgene— represents a safe alternative to the use of the extremely toxic phosgene — $\text{Cl}_2\text{CO}$ —. Both consist in a carbonyl group linked to two good-leaving groups.

1– The amine reacts with the carbonyl group in triphosgene and expels a trichloromethoxy anion.

2– The resulting intermediate containing the group  $\text{R-NH}(\text{C}=\text{O})\text{OCCl}_3$ , is attacked by the carboxylic acid on the carbonyl group and a trichloromethoxy anion is again expelled.

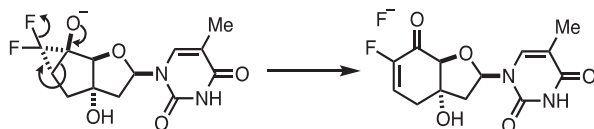


Jentsch, N.G.; Hume, J.D.; Crull, E.B.; Beauti, S.M.; Pham, A.H.; Pigza, J.A.; Kessl, J.J.; and Donahue, M.G., *Beilstein J.Org.Chem.* **14**, 2529 (2018)

## Exercise 45

1– Hydrofluoric acid produces the deprotection of both silyl groups, a reaction facilitated by the formation of strong fluor-silicon bonds.

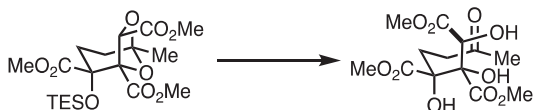
2– The base pyridine forms and alkoxide that evolves by an electron flow that results in the opening of the very strained three-membered ring and the expulsion of a fluoride anion.



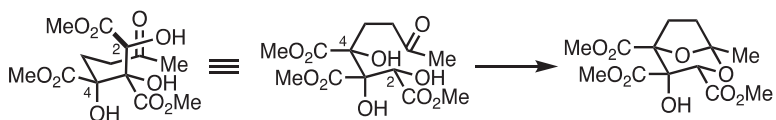
Frei, S.; Istrate, A.; and Leumann, C.J., *Beilstein J.Org.Chem.* **14**, 3088 (2018)

### Exercise 46

1– Trifluoroacetic acid produces the hydrolyses of the silyl ether and the acetal.



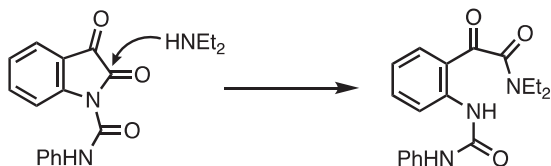
2– A new acetal is formed by reaction of the alcohols in positions 2 and 4 with the ketone.



Sintim, H.O.; Al Mamari, H.H.; Almohseni, H.A.A.; Fegheh-Hassanpour, Y.; and Hodgson, D.M., *Beilstein J.Org.Chem.* **15**, 1194 (2019)

### Exercise 47

1– Diethylamine attacks one of the carbonyls of the starting isatin producing the opening of the five-membered ring.



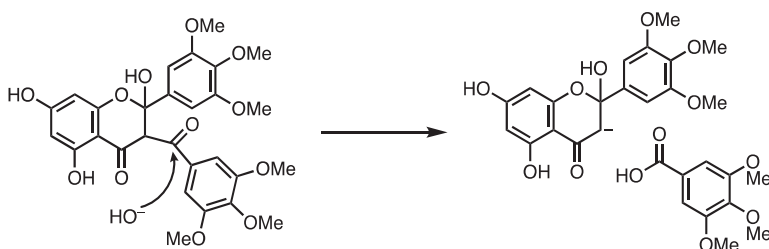
2– One of the nitrogens of the urea attacks the ketone.

Aziza, M.N.; Panda, S.S.; Shalaby, E.M.; Fawzy, N.G.; and Girgis, A.S., *RSC Adv.* **9**, 28534 (2019)

## Exercise 48

It goes without saying that the mechanism does not consist on hydroxide attack on the aliphatic ketone with ousting of a vinylic anion. This anion would be notably unstable because it seats on an  $sp^2$  carbon and no stabilization by conjugation with the neighbouring ketone is possible as there is an absence of proper overlap of orbitals.

- 1– Hydroxide adds to the alkene conjugated with two ketones.
- 2– Another hydroxide anion attacks the aliphatic ketone and expels an enolate via an addition-elimination mechanism.

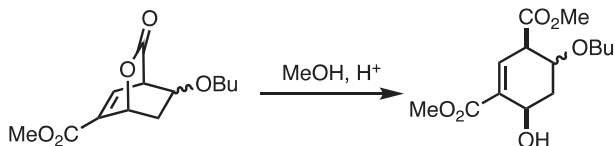


- 3- Hydroxide is expelled by an  $E_{1cB}$  mechanism.

Zhang, W.; Xue, W.; Jia, Y.; Wen, G.; Lian, X.; Shen, J.; Liu, A.; and Wu, S., *RSC Adv.* **8**, 14389 (2018)

## Exercise 49

- 1– Methanol reacts with the lactone via an acid-catalysed transesterification, yielding a methyl ester and an alcohol.



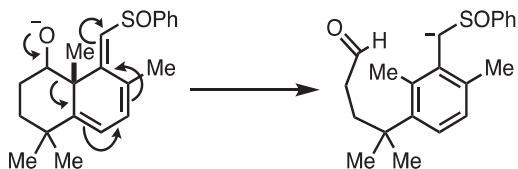
- 2– Acid-catalysed dehydration and elimination of the ether —boosted by aromatization— provides the final product.

Kraus, G.A.; and Wang, S., *RSC Adv.* **7**, 56760 (2017)



### Exercise 50

- 1-  $\text{LiAlH}_4$  attacks the acetate producing the release of an alkoxide anion.
- 2- The alkoxide anion evolves by generating an aldehyde and a carbanion stabilised by extended conjugation, including a resonant form with the anion located on  $\alpha$  to the sulfoxide and an aromatic ring. This fragmentation is greatly facilitated by the generation of aromaticity.



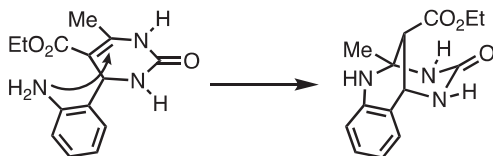
- 3-  $\text{LiAlH}_4$  reduces the aldehyde to alcohol and the sulfoxide to sulfide.

Khodabocus, A, *Arkivoc*, **6**, 854 (2000)

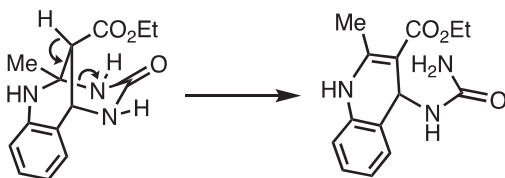
### Exercise 51

The authors propose the following mechanism for this intriguing transformation:

- 1- The amino group exerts an intramolecular aza-Michael addition to the unsaturated ethyl ester.



- 2- One of the nitrogens in the urea is detached by a retro-Michael elimination with recovering of the olefin in the unsaturated ester.



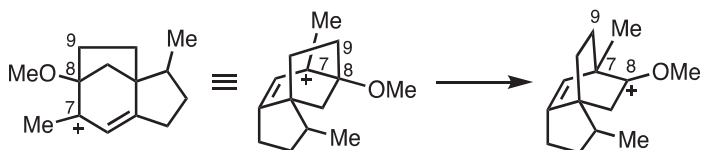
3– Elimination of  $\text{H}_2\text{NCONH}_2$  leads to aromatization to the final quinoline, an aromatization that provides the driving force for the entire transformation.

Stiasni, N.; and Kappe, C.O., *Arkivoc*, **8**, 71 (2002)

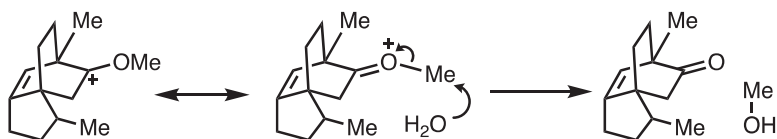
## Exercise 52

1– The alcohol, protonated by  $\text{HClO}_4$ , loses water resulting in a carbocation at C-7 that is stable because it is tertiary and allylic.

2– The C-9 carbon shifts to the carbocation on C-7, leaving a carbocation at C-8 very well stabilized by the adjacent oxygen atom.



3– The carbocation at C-8 can be expressed as a resonance form consisting in an oxonium ion. This oxonium ion can be envisaged as an *O*-methylated ketone. This *O*-methylated ketone loses the methyl by assistance by a water molecule from the perchloric acid solution.

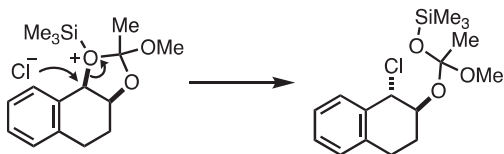


Biju, P.J.; Pramod, K.; and Subba Rao, G.S.R., *Arkivoc*, **3**, 88 (2003)

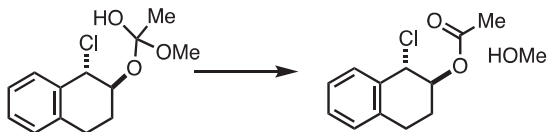
### Exercise 53

1– The oxygen at the benzylic position attacks the silicon atom in  $\text{TMSCl}$  producing a  $\text{R}_2\text{O}^+\text{SiMe}_3$  cation and  $\text{Cl}^-$ .

2– Chloride attacks the carbon at the benzylic position via a  $\text{S}_{\text{N}}2$  reaction with the  $\text{R}_2\text{O}^+\text{SiMe}_3$  oxygen operating as a good leaving group. As a result, chloride enters the benzylic position with inversion of configuration and a  $\text{ROC}(\text{OTMS})(\text{OMe})\text{Me}$  moiety is formed. The reaction happens at the benzylic position because the energy of the transition state for the  $\text{S}_{\text{N}}2$  reaction is lowered by delocalization of charge by conjugation with the aromatic ring.



3– Probably during work-up with water, the trimethylsilyl ether in  $\text{ROC}(\text{OTMS})(\text{OMe})\text{Me}$  is broken, leading to an intermediate  $\text{ROC}(\text{OH})(\text{OMe})\text{Me}$  that evolves to an acetate with delivery of methanol.

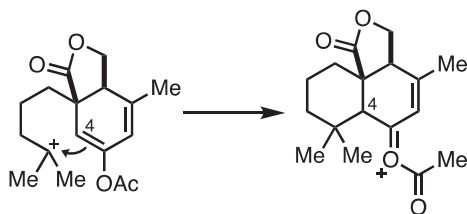


Boyd, D.R.; Sharma, N.D.; Kerley, N.A.; McConville, G.; Allen, C.C.R.; and Blacker, A.J., *Arkivoc*, **7**, 32 (2003)

### Exercise 54

1– A stable tertiary carbocation is formed by protonation of the alkene in the 4-methyl-pent-3-enyl chain.

2– The enol acetate reacts with this carbocation by attack by the C-4 carbon.



3– This results in a carbocation that can be described as a positively charged *O*-acetylated ketone that is hydrolysed to the final ketone.

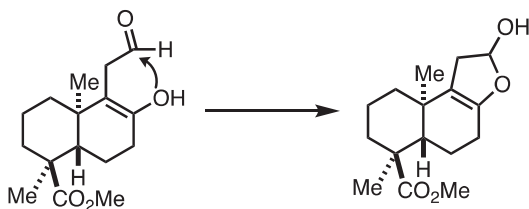
Watanabe, H.; Yamaguchi, T.; Furuuchi, T.; Kido, M.; Bando, M.; and Kitahara, T., *Arkivoc*, **8**, 267 (2003)

### Exercise 55

During the attempted protection of an aldehyde as an ethylidene acetal, a furan ring is formed.

1– The ketone tautomerizes to enol.

2– The oxygen in the enol attacks intramolecularly the aldehyde producing a cyclic hemiacetal.



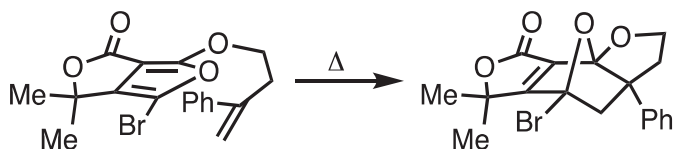
3– Dehydration of the hemiacetal leads to a furan ring that is stable due to aromaticity.

Rosana A. Giacomini, R.A.; de L. Miranda, P.C.M.; Lúcia H. B. Baptistella, L.H.B.; and Imamura, P.M., *Arkivoc*, **10**, 314 (2003)

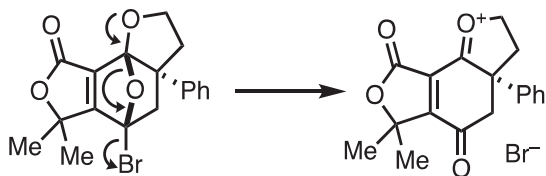
### Exercise 56

A labyrinthine skeletal metamorphosis can be explained with only three steps and two intermediates.

1– There is an intramolecular Diels-Alder reaction where the furan operates as the diene.



2– A bromide ion is expelled thanks to an electron movement that begins in an oxygen and causes the breakage of a C–O bond.



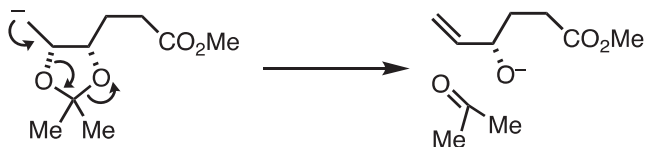
3– Finally, the bromide anion operates as a nucleophile in an  $S_N2$  reaction in which an oxonium ion functions as a good-leaving group.

Padwa, A.; Crawford, K.R.; and Straub, C.S., *Arkivoc* **8**, 14 (2007)

### Exercise 57

1– Zinc inserts into the C-I bond generating an organometallic compound R-CH<sub>2</sub>-Zn-I.

2– As a simplification, we may envision the carbon in the highly polarized C-Zn bond as behaving like a nude carbanion. This unstable carbanion evolves producing the breakage of the dioxolane with formation of an alkene, evolution of acetone and generation of an alkoxide.



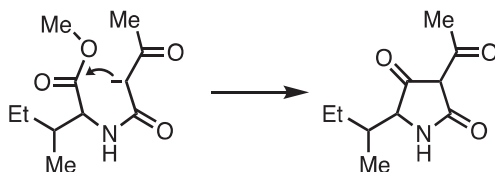
3– A  $\gamma$ -lactone is formed by attack of the resulting alkoxide on the ester.

Totokotsopoulos, S.M.; Anagnostaki, E.E.; Stathakis, C.I.; Yioti, E.G.; Hadjimichael, C.Z.; and Gall, J.K., *Arkivoc*, **10**, 209 (2009)

### Exercise 58

1– Sodium methoxide generates an anion stabilized by the carbonyl groups of the amide and the ketone.

2– This anion reacts intermolecularly with the ester displacing the methoxy group.



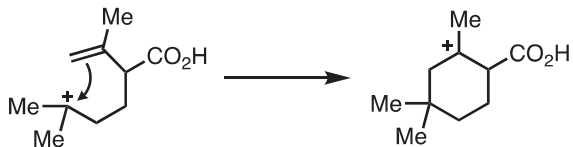
3– The methyl ketone tautomerizes to the enol, which is stable due to conjugation with two carbonyls.

Wang, X.-F.; Si, T.-F.; Li, Q.-B.; Zhu, Z.-Y.; Zhu, X.-J.; Qiang, S.; and Yang, C.-L., *Arkivoc*, **2**, 31 (2010)

### Exercise 59

1– The more electron-rich trisubstituted alkene is protonated yielding a stable tertiary carbocation.

2– The other alkene attacks this tertiary carbocation resulting in the formation of the cyclohexane and another tertiary carbocation.

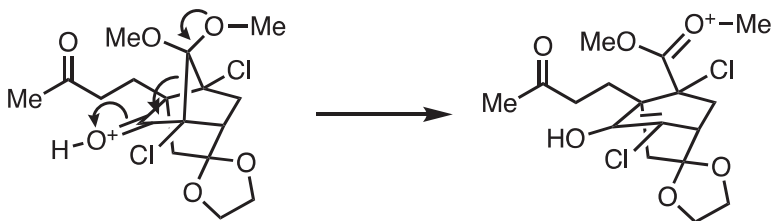


3– Loss of a proton leads to the formation of an alkene stabilized by conjugation with the carboxylic acid.

Fröhner, W.; R. Reddy, K.R.; and Knölker, H.-R., *Arkivoc*, **3**, 330 (2012)

### Exercise 60

1– Protonation of one of the ketones prepares the following fragmentation:



2– The resulting enol tautomerizes to ketone with racemization at the  $\alpha$  position.

3– The methyl attached to the oxonium group is removed by attack by adventitious water or the *p*-tosylate anion.

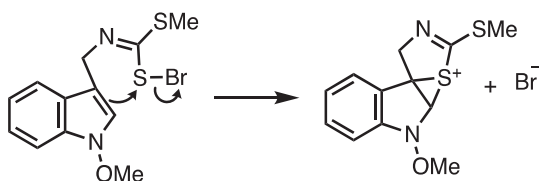
Khan, F.A.; and Budanur, B.M., *Arkivoc*, **2**, 206 (2016)

## Exercise 61

1– Bromination of sulfur produces an intermediate with a sulfur-bromine bond with a very electrophilic sulfur atom.



2– Attack of the enamine on sulfur leads to a sulfonium cation in a three-membered ring.



3– Finally, opening of the unstable three-membered ring by methanol yields the product.

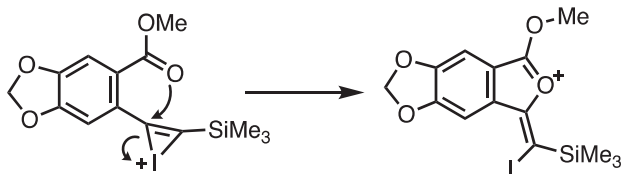
Budovská, M.; Pilátová, M.B.; Tischlerová, V.; and Mojžiš, J., *Arkivoc*, **6**, 198 (2016)



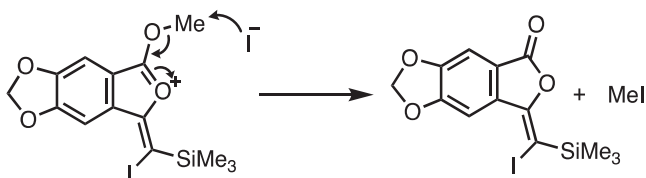
## Exercise 62

1– Iodine reacts with the alkyne leading to the formation of an iodonium ion in a three-membered ring.

2– The oxygen in the carbonyl of the ester expels the positively charged iodine atom.



3– Finally an iodide cation removes a methyl group.

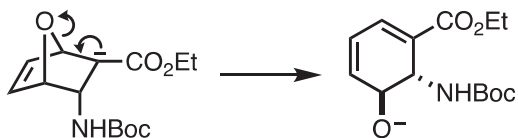


Moore, C.A.; Ohman, B.F.; Garman, M.J.; Liquori, M.E.; David M. Degan, Voellinger, K.B.; DePersis, M.J.; and Pelkey, E.T., *Arkivoc*, **4**, 50 (2018)

## Exercise 63

1– The strong base KHMDS forms an anion on  $\alpha$  to the ester carbonyl.

2– This anion evolves by formation of an alkene with expulsion an alkoxide.



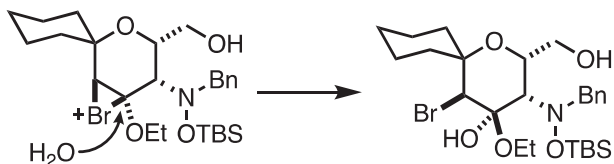
3– Protonation of the alkoxide yields the product.

Masesane I.B.; Batsanov, A.S.; Howard, J.A.K.; Mondal, R.; and Steel, P.G., *Beilstein J.Org.Chem.* **2**, No 8 (2006)

**Exercise 64**

1– The enol ether attacks the electrophilic bromine in NBS producing a bromonium ion in a three-membered ring.

2– Water displaces the bromine with an  $S_N2$  reaction.



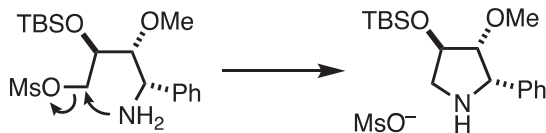
3– The resulting hemiacetal loses ethanol to give a ketone.

Pfrefre, F.; and Reissig, H.-U., *Beilstein J.Org.Chem.* **6**, No 75 (2010)

**Exercise 65**

1– Mesyl chloride in the presence of triethylamine produces the mesylation of the alcohol via the intermediate  $H_2C=SO_2$ .

2– The nitrogen displaces the mesylate generating a pyrrolidine ring

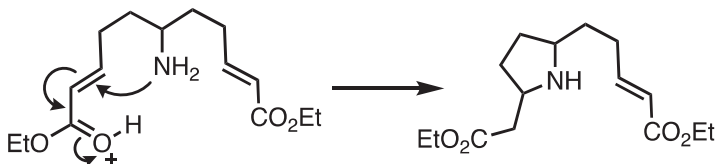


3– At some point the amine is mesylated.

Jasiński, M.; Lentz, D.; and Reissig, H.-U., *Beilstein J.Org.Chem.* **8**, 662 (2012)

### Exercise 66

- 1- Trifluoroacetic acid produces the deprotection of the Boc group.
- 2- Protonation of one of the esters activates one of the alkenes for an intramolecular Michael addition by the amine.

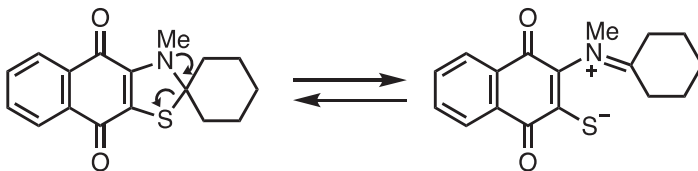


- 3- A similar reaction on the other ester gives the final product.

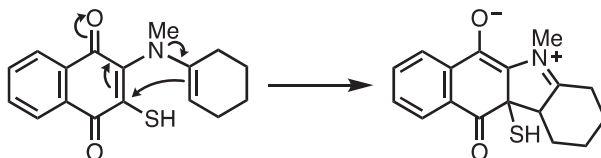
O'Connell, K.M.G.; Díaz-Gavilán, M.; Galloway, W.R.J.D., and Spring, D.R. *Beilstein J.Org.Chem.* **8**, 850 (2012)

### Exercise 67

- 1- The thiazole equilibrates with a zwitterionic compound with positive charge on the nitrogen and negative charge on the sulfur.



- 2- Transprotonation to sulfur leads to an enamine that attacks via carbon the olefin activated by conjugation with two ketones.

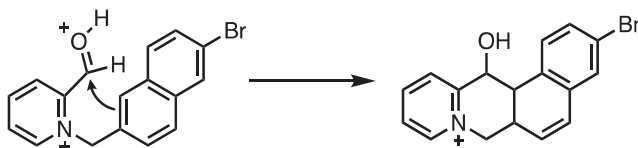


- 3- Expulsion of sulfide and deprotonation leads to the final product.

Konstantinova, L.S.; Lysov, K.A.; Souvorova, L.I.; and Rakitin, O.A., *Beilstein J.Org.Chem.* **9**, 577 (2013)

**Exercise 68**

- 1– Acidic hydrolysis of the acetal liberates an aldehyde.
- 2– The protonated aldehyde is attacked by the naphthalene ring in an aromatic electrophilic substitution.

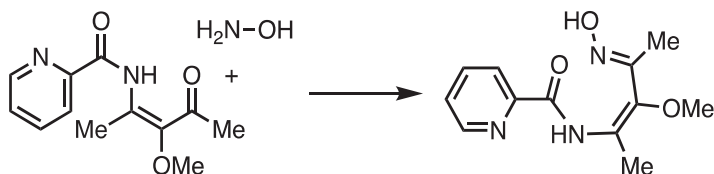


- 3– Protonation of the alcohol is followed by dehydration and aromatization to the final compound.

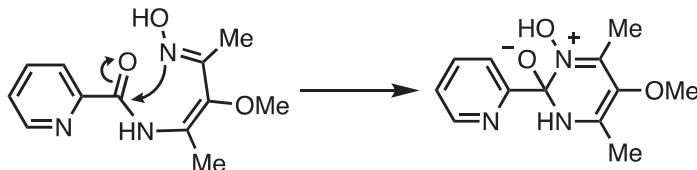
Pithan, P.M.; Decker, D.; Sardo, M.S.; Viola, G.; and Ihmels, H., *Beilstein J.Org.Chem.* **12**, 854 (2016)

**Exercise 69**

- 1– Condensation of hydroxylamine with the ketone delivers an oxime.



- 2– The nitrogen of the oxime attacks the carbonyl of the amide.



- 3– Transprotonations and dehydration produce an aromatic pyrimidine *N*-oxide.

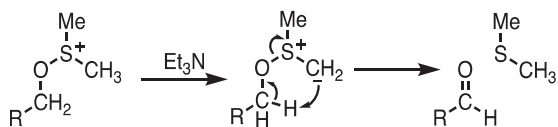
Hommel, P.; and Reissig, H.-U., *Beilstein J.Org.Chem.* **12**, 1170 (2016)

## Exercise 70

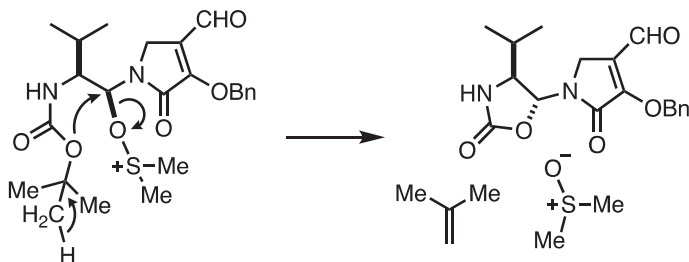
During a Swern oxidation of alcohol to aldehyde, a cyclic carbamate is formed.

1– In compliance with the accepted mechanism for the Swern oxidation, reaction of oxalyl chloride with dimethyl sulfoxide gives the activated sulfonium species  $\text{Me}_2\text{S}^+\text{Cl}$ .

2– Reaction of  $\text{Me}_2\text{S}^+\text{Cl}$  with the primary alcohol gives a compound  $\text{R-CH}_2\text{-O-S}^+\text{Me}_2$  that suffers elimination under the effect of triethylamine delivering an aldehyde.



3– On an unanticipated development, the hydroxy group of the aminal is activated by reaction with  $\text{Me}_2\text{S}^+\text{Cl}$  and is displaced via an  $\text{S}_{\text{N}}2$  reaction by the neighbouring carbamate with inversion of configuration.

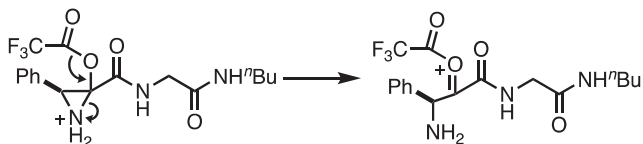


Dhavan, A.A.; Kaduskar, R.D.; Musso, L.; Scaglioni, L.; Martino, P.A.; and Dallavalle, S., *Beilstein J.Org.Chem.* **12**, 1624 (2016)

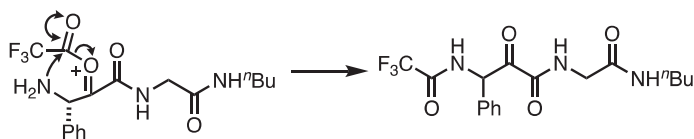
## Exercise 71

1– Protonation of the methoxy group allows its departure with substitution with an entering trifluoroacetate, either by an  $S_N1$  or an  $S_N2$  mechanism.

2– The aziridine is opened after protonation of the nitrogen thanks to the assistance of the trifluoroacetate.



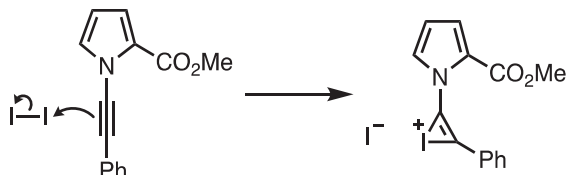
3– The amine is intramolecularly trifluoroacetylated.



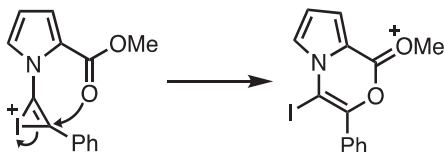
Huck, L.; González, J.F.; de la Cuesta, E.; and Menéndez, J.C., *Beilstein J.Org.Chem.* **12**, 1772 (2016)

**Exercise 72**

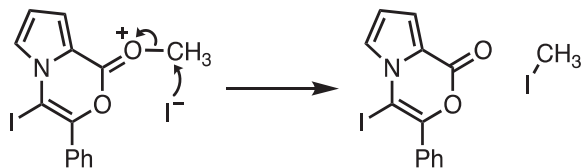
1– Molecular iodine reacts with the alkyne forming an iodonium intermediate inside a three-membered ring.



2– The oxygen in the carbonyl attacks the three-membered ring with the iodonium cation working as a leaving group.



3– The iodide anion attacks the methyl group delivering the final product.

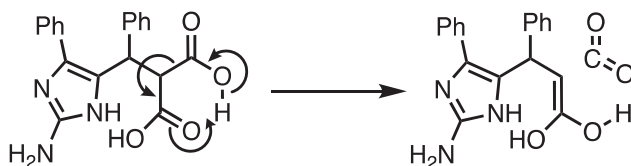


Yenice, I.; Basceken, S.; and Balci, M., *Beilstein J.Org.Chem.* **13**, 825 (2017)

### Exercise 73

1– Trifluoroacetic acid removes the isopropylidene group giving a geminal diol on an  $sp^2$  carbon that tautomerizes to a carboxylic acid

2– The resulting dicarboxylic acid suffers a very easy decarboxylation with evolution of carbon dioxide because both acids are located at a relative  $\beta$  position, thus allowing a low-energy six-membered transition state.



3– Finally, condensation of a nitrogen from the imidazole with the carboxylic acid yields a lactam.

Lipson, V.V.; Pavlovska, T.L.; Svetlichnaya, N.V.; Poryvai, A.A.; Gorobets, N.Y.; Van der Eycken, E.V.; Kononova, I.S.; Shiskina, S.V.; Borisov, A.V.; Musatov, V.I.; and Mazepa, A.V., *Beilstein J.Org.Chem.* **15**, 1032 (2019)



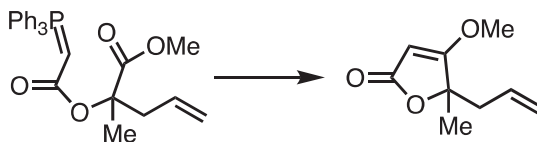
## Exercise 74

Normally the carbonyl group of esters does not react with Wittig reagents because of lack of reactivity as compared with aldehydes and ketones. In this case, this reaction is possible on account of the favourable formation of a five-membered ring.

1– Triphenylphosphine expels the bromine resulting in a phosphonium salt.

2– Deprotonation of the phosphonium salt with the amine leads to a Wittig reagent.

3– The Wittig reagent condenses intramolecularly with the carbonyl of the ester.

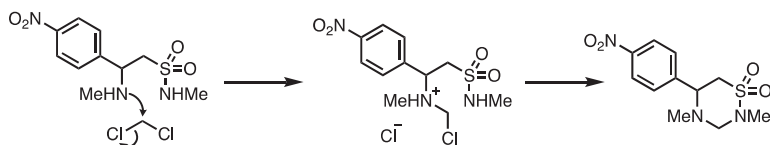


Monjas, L.; Fodran, P.; Kollback, J.; Cassani, C.; Olsson, T.; Genheden, M.; Larsson, D.G.J.; and Wallentin, C.-J., *Beilstein J.Org.Chem.* **15**, 1468 (2019)

## Exercise 75

This is an interesting example in which dichloromethane, a very common solvent, plays a role as reagent.

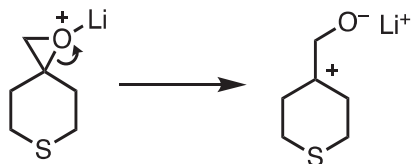
- 1– One molecule of methylamine makes a conjugated addition to the unsaturated sulfonyl fluoride.
- 2– Another molecule of methylamine substitutes the fluoride by an addition-elimination mechanism on the sulfonyl fluoride.
- 3– Each one of the nitrogen atoms displaces a chlorine atom in dichloromethane via an  $S_N2$  reaction.



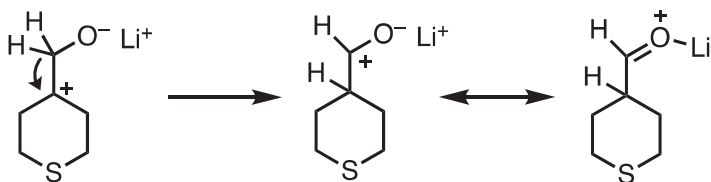
Khumalo, M.M.; Akpan, E.D.; Chinthakindi, P.K.; Brasil, E.M.; Rajbongshi, K.K.; Makatini, M.M.; Govender, T.; Kruger, H.G.; Naicker, T.; and Arvidsson, P.I., *RSC Adv.* **8**, 37503 (2018)

**Exercise 76**

- 1– The oxygen in the epoxide is activated by complexation with  $\text{Li}^+$ .
- 2– The epoxide opens producing a lithium alkoxide and a stable tertiary carbocation.



- 3– One of the hydrogens on  $\alpha$  to the oxygen migrates to the carbocation. This produces a carbocation on  $\alpha$  to the oxygen that can be represented in a different resonance form as an aldehyde complex with  $\text{Li}^+$ .



- 4– Removal of  $\text{Li}^+$  yields the final aldehyde.

Fröhlich, J.; Sauter, F.; Hametner, C.; and Pfalz, M., *Arkivoc*, **6**, 298 (2009)

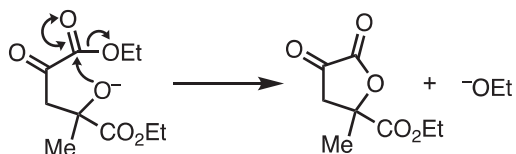
## Exercise 77

Dimerization of ethyl pyruvate under basic conditions is followed by *in situ* *O*-alkylation.

1– The enolate of ethyl pyruvate is generated under basic conditions.

2– It condensates with the ketone of a second ethyl pyruvate molecule leading to an alkoxide.

3– The alkoxide leads to a lactone by displacement of an ethoxy group from an ester.

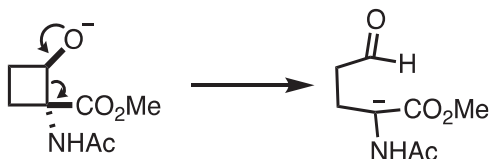


4– The enolate of the ketone is *O*-alkylated by ethyl tosylate.

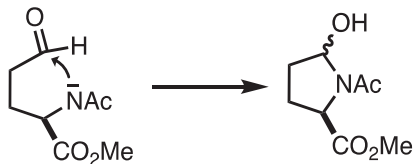
Chen, H.; Ma, X.; Li, Z.; Wang, Q.; and Tao, F., *Arkivoc*, **10**, 87 (2009)

## Exercise 78

- 1- Sodium hydride generates an alkoxide anion.
- 2- This alkoxide evolves by formation of an aldehyde and a carbanion stabilized by the carbonyl group with fragmentation of the cyclobutane ring. This reverse of the addition of an enolate to an aldehyde is favoured by the release of ring tension.



- 3- A number of protonations and deprotonations lead to an anion on the nitrogen.
- 4- This anion attacks the aldehyde intramolecularly yielding an iminal and a stable five-membered ring.



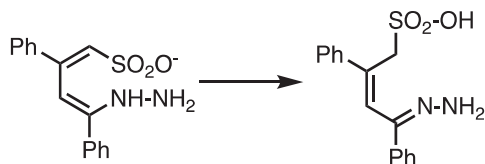
Pérez-Fernández, M.; Avenoza, A.; Busto, J.H.; Peregrina, J.M.; and Rodríguez, F., *Arkivoc*, **3**, 191 (2010)

## Exercise 79

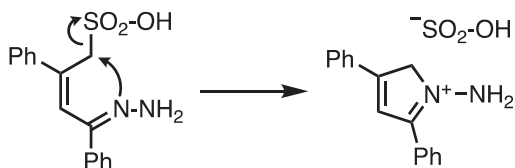
In this transformation, we need to apply basic reactivity principles to uncommon functional groups. First we have a conjugated addition at the  $\delta$  position of an unsaturated sulfonate on an olefin rendered electron-poor by conjugation with a  $-\text{SO}_3\text{OR}$  group, rather than the more common carbonyl group. Then we have the sulfur in the bisulfate anion,  $^-\text{SO}_2\text{OH}$ , acting as a good-leaving group, rather than a more common sulfonate,  $\text{R-SO}_2\text{O}^-$ .

1– There is a nucleophilic attack of hydrazine on the  $\delta$  position of the unsaturated sulfonate with ensuing removal of sulfonate operating as a leaving group.

2– The resulting intermediate evolves by protonations and deprotonations to a hydrazone.



3– There is a ring closure by a  $\text{S}_{\text{N}}2$  displacement of bisulfate by nitrogen.



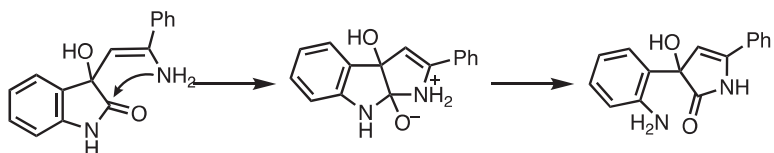
4– The iminium salt tautomerizes to the final aromatic compound.

Ali, K.A.; Jäger, A.; and Metz, P., *Arkivoc*, **3**, 14 (2016)

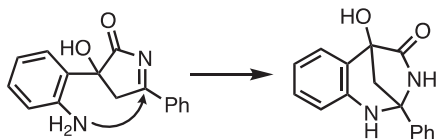
## Exercise 80

1– Ammonia reacts with the ketone yielding an enamine.

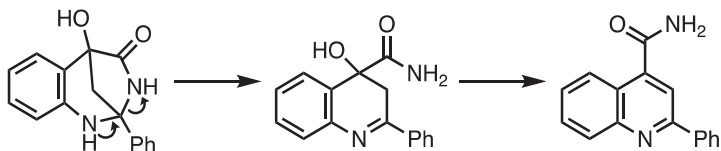
2– The nitrogen of the enamine reacts with the carbonyl of the lactam and breaks the amide bond.



3– The olefin is isomerized into conjugation with the carbonyl producing a C=N bond that is attacked by the amine.



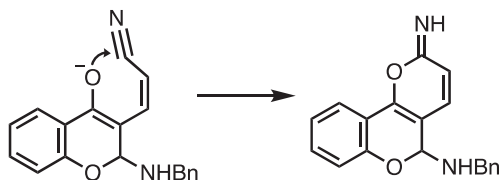
4– Breakage of the gem-diamine followed by dehydration of the alcohol leads to the final compound.



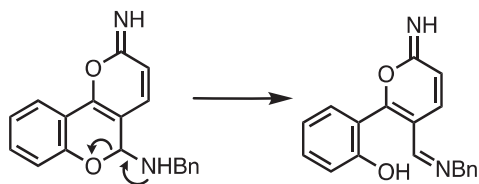
Tiwari, K.N.; Choubey, R.; Shukla, S.; and Gautam, P., *Arkivoc*, **3**, 165 (2018)

## Exercise 81

- 1– Michael addition of the amine on the enone leads to an enolate.
- 2– The resulting enolate attacks the cyanide after isomerization of an alkene to the (*cis*) form.



- 3– Fragmentation of the hemiaminal ether liberates a phenol.



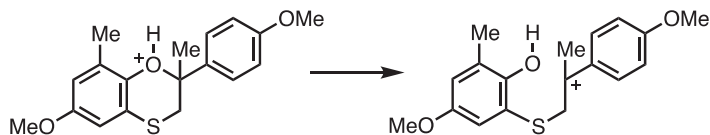
- 4– Transamination of the imidate with release of ammonia yields the final compound.

Ibrahim, M.A.; and Badran, A.-S.; *Arkivoc*, 7, 214 (2018)

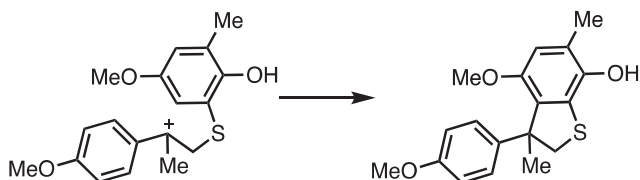


## Exercise 82

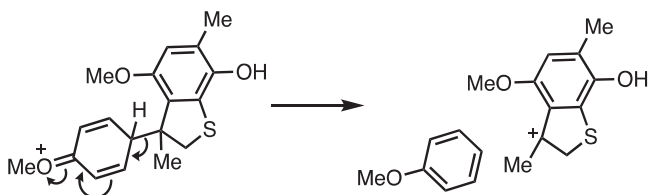
1– Protonation of the central ether leads to a fragmentation resulting in a carbocation that is stable due to being tertiary, benzylic and probably in equilibrium with a sulfonium cation in a three-membered ring.



2– This cation participates in a Friedel-Crafts alkylation of the phenolic aromatic ring.



3– Protonation of the anisole moiety is followed by detachment of anisole and formation of a stable carbocation.

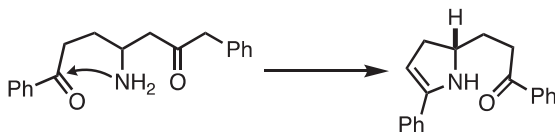


4– Deprotonation of this carbocation leads to the product.

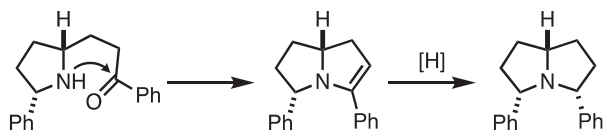
Viglianisi, C.; Di Pietro, L.; Meoni, V.; Amorati, R.; Menichetti, S., *Arkivoc*, **2**, 65 (2019)

**Exercise 83**

- 1- The nitro group is reduced to amine by catalytic hydrogenation.
- 2- Condensation of the amine with one of the ketones gives an enamine.



- 3- The enamine is reduced to amine.
- 4- The resulting amine condensates with the remaining ketone forming an enamine that is reduced to amine.

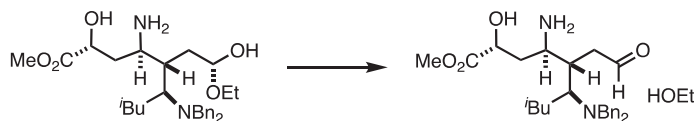


O'Connell, K.M.G.; Díaz-Gavilán, M.; Galloway, W.R.J.D., and Spring, D.R. *Beilstein J.Org.Chem.* **8**, 850 (2012)

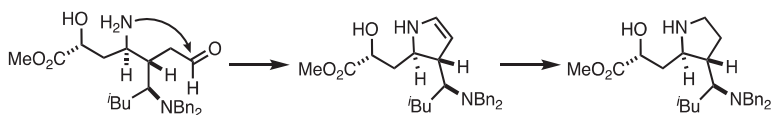
## Exercise 84

1– Hydrogenolysis by catalytic hydrogenation of both nitrogen-oxygen bonds leads to an amine, an alcohol and a hemiacetal.

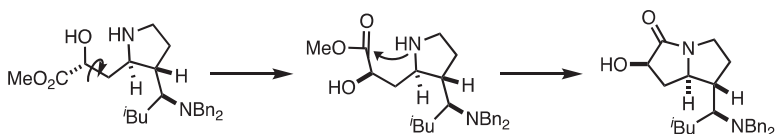
2– The hemiacetal generates an aldehyde after losing ethanol.



3– The amine condenses with the aldehyde forming an enamine that is reduced by catalytic hydrogenation resulting in the formation of a pyrrolidine.



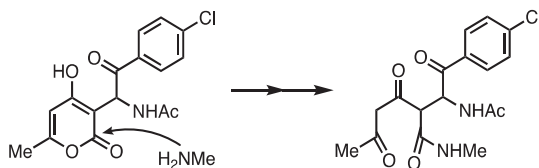
4– The nitrogen of the pyrrolidine attacks the methyl ester. This leads to the formation of a lactam.



de Carvalho, L.L.; Burrow, R.A.; and Pereira, V.L.P., *Beilstein J.Org.Chem.* **9**, 838 (2013)

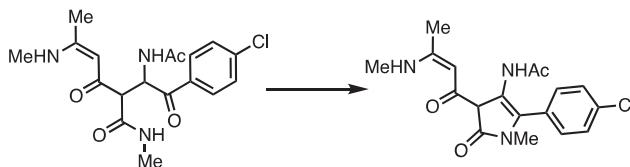
## Exercise 85

1– Methylamine attacks the carbonyl of the lactone delivering an amide and a diendiol that tautomerizes to a diketone.



2– Methylamine reacts with the methyl ketone generating an enamine.

3– The nitrogen of the *N*-methylamide reacts with the aryl ketone giving an enamine.



4– Migration of the alkene of the enamine into conjugation with both carbonyls gives the final compound.

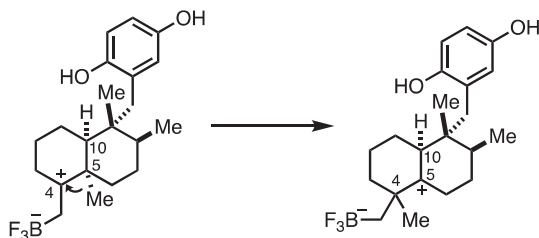
Melekhina, V.G.; Komogortsev, A.N.; Lichitsky, B.V.; Mityanov, V.S.; Fakhruddinov, A.N.; Dudinov, A.A.; Migulin, V.A.; Nelyubina, Y.V.; Melnikova, E.K.; and Krayushkin, M.M., *Beilstein J.Org.Chem.* **15**, 2840 (2019)

## Exercise 86

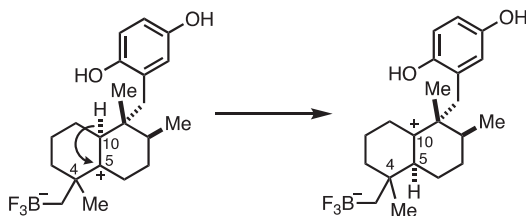
A carbocation migrates from C-4 to C-10 by a cascade of atom shifts.

1–  $\text{BF}_3$  reacts with the alkene generating a stable tertiary carbocation at C-4 and a negatively charged  $\text{R-CH}_2\text{-B-F}_3$  unit at the terminal carbon.

2– The methyl group at C-5 migrates to the carbocation at C-4 leading to a carbocation at C-5.



3– The hydrogen at C-10 migrates to the carbocation at C-5 leading to a carbocation at C-10.



4– The carbocation at C-10 is trapped by the proximal phenol.

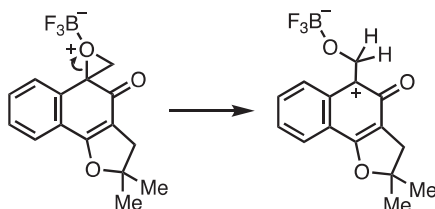
5– The carbon in the  $\text{R-CH}_2\text{-B-F}_3$  unit is protonated during work-up.

Nakatani, M.; Nakamura, M.; Suzuki, A.; Fuchikami, T.; Inoue, M.; and Katoh, T., *Arkivoc*, **8**, 45 (2003)

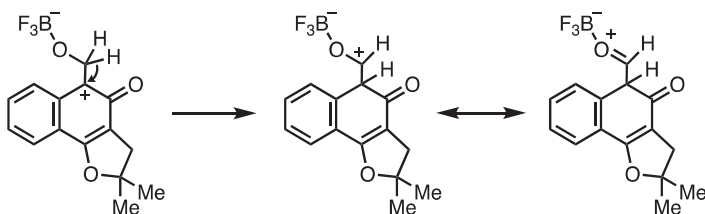
## Exercise 87

1–  $\text{BF}_3$  forms the complex  $\text{R}_2\text{O}^+-\text{B}-\text{F}_3$  with the oxygen of the epoxide.

2– This promotes the release of the strain of the three-membered ring by opening of the epoxide to  $\text{R}_2\text{C}^+-\text{CH}_2\text{O}-\text{B}-\text{F}_3$ .



3– A hydrogen migration transforms  $\text{R}_2\text{C}^+-\text{CH}_2\text{O}-\text{B}-\text{F}_3$  into  $\text{R}_2\text{CH}-\text{C}^+\text{HO}-\text{B}-\text{F}_3$ . Observe that  $\text{R}_2\text{CH}-\text{C}^+\text{HO}-\text{B}-\text{F}_3$  is in fact an aldehyde complexed with  $\text{BF}_3$ .



Note: steps 2 and 3 involve the intermediacy of a carbocation located on  $\alpha$  to a ketone, a highly unstable carbocation if it ever exists as a minimum of energy. It is possible to avoid the intermediacy of this unstable carbocation by postulating the migration of hydrogen synchronous with the opening of the three-membered ring.

4– The ketone tautomerizes to the enol, a process driven by gain in aromaticity.

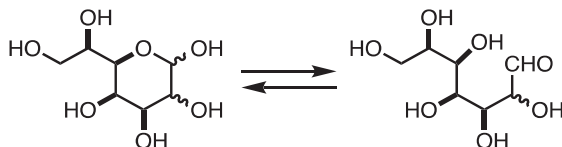
5– Probably during the elaboration, the boron complex is broken leading to the liberation of the aldehyde.

da Silva, M.N.; da Souza, M.C.B.V.; Ferreira, V.F.; Pinto, A.V.; Pinto, M.C.R.F.; Wardell, S.M.S.V.; and Wardell, J.L., *Arkivoc*, **10**, 156 (2003)

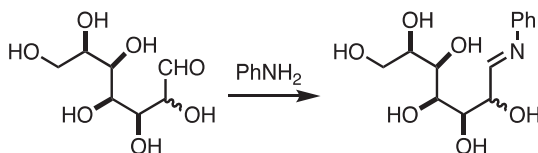
## Exercise 88

This is an example of the so-called Amadori rearrangement in which the *N*-glycoside of an aldose is transformed into a 1-aminoketose.

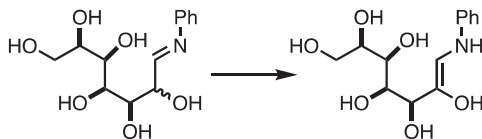
1– The starting cyclic hemiacetal equilibrates with the open form containing an aldehyde.



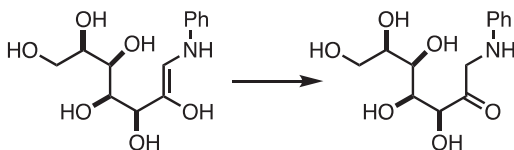
2– The aldehyde condenses with aniline forming an imine.



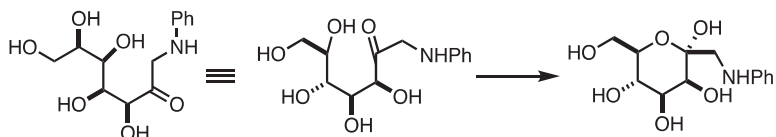
3– The imine tautomerizes to enamine.



4– The enamine contains an enol moiety that tautomerizes to an  $\alpha$ -ketoamine.



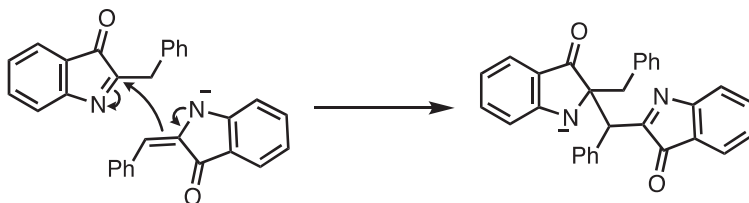
5– The ketone forms a cyclic hemiacetal by reaction with one of the hydroxy groups.



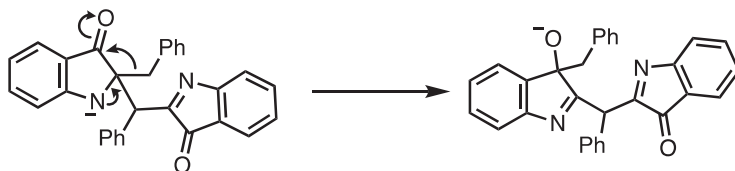
Gloe, T.-E; Stamer, I.; Hojnik, C.; Wrodnigg, T.M.; and Lindhorst, T.K.,  
*Beilstein J.Org.Chem.* **11**, 1096 (2015)

## Exercise 89

1– There is a dimerization in which one molecule loses a proton and becomes a nucleophile, while other molecule suffers the migration of a double bond leading to an imine that behaves as an electrophile.



2– The resulting amide anion evolves as the origin of an electron flow that causes the migration of the benzyl group to the ketone yielding an alkoxide.

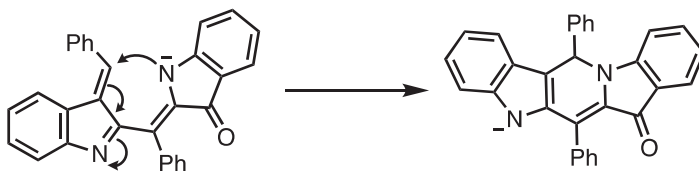


3– The alkoxide is protonated to alcohol and the alcohol suffers base-catalysed dehydration, yielding an olefin that is electrophilic because it is conjugated with an imine.

4– Deprotonation at the carbon located at the  $\alpha$  position of both imines gives rise to a delocalized anion with a resonance structure with the negative charge located at one of the nitrogens.



5– This nitrogen attacks the electron-poor alkene.



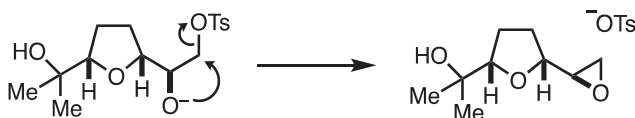
6– Finally, the product is obtained by protonation of the resulting amide anion.

Velezheva, V.S.; Babii, O.L.; Khodak, A.A.; Alekseeva, E.A.; Nelyubina, Y.V.; Godovikov, I.A.; Peregudov, A.S.; Majorov, K.B.; and Nikonenko, B.V., *RSC Adv.* **9**, 41402 (2019)

## Exercise 90

1– TsCl produces the selective monotosylation of the less hindered primary alcohol.

2– The base DBU generates an alkoxide on the secondary alcohol that displaces the neighbouring tosylate by a  $S_N2$  reaction.

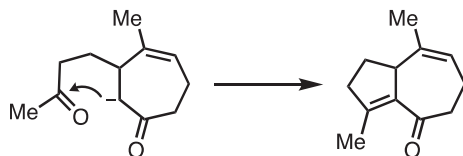


Cecil, A.R.L.; and Brown, R.C.D., *Arkivoc*, **11**, 49 (2001)

## Exercise 91

1– Acid hydrolysis of the cyclic acetal liberates a ketone. Acetone is used as solvent as it reacts with the released 1,2-ethanediol forming the corresponding acetal and therefore drives the equilibrium to the deprotection of the desired ketone.

2– Aldol condensation between the methyl ketone and the cycloheptanone gives the final compound.

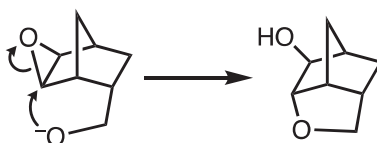


Cheong, J.Y.; and Rhee, Y.H., *Beilstein J.Org.Chem.* **7**, 740 (2011)

## Exercise 92

1– *m*-Chloroperbenzoic acid epoxidizes the alkene on the less hindered side.

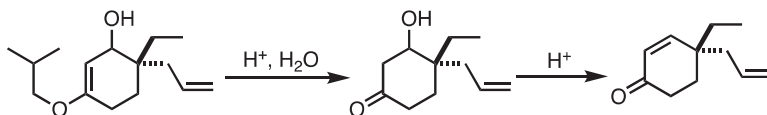
2– Under basic conditions, an alkoxide is formed that attacks the epoxide.



Bailey, W.F.; and Fair, J.D., *Beilstein J.Org.Chem.* **9**, 537 (2013)

### Exercise 93

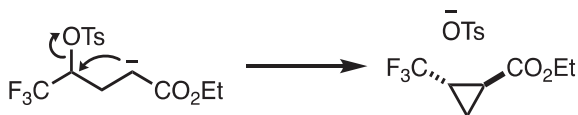
- 1– Lithium aluminium hydride reduces the ketone to alcohol.
- 2– Hydrochloric acid catalyses the hydrolysis of the enol ether to ketone and the dehydration of the alcohol to give an alkene conjugated with the ketone.



Liu, Y.; Liniger, M.; McFadden, R.M.; Roizen, J.L.; Malette, J.; Reeves, C.M.; Behenna, D.C.; Seto, M.; Kim, J.; Mohr, J.T.; Virgil, S.C.; and Stoltz, B.M., *Beilstein J.Org.Chem.* **10**, 2501 (2014)

### Exercise 94

- 1– Potassium *tert*-butoxyde generates a carbanion on the  $\alpha$  position of the ester. This carbanion displaces the tosylate resulting in the formation of a cyclopropane

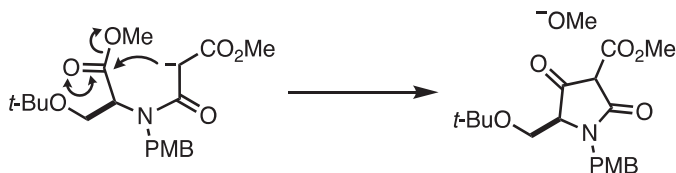


- 2– Addition of water to the anhydrous basic medium allows the basic hydrolysis of the ester to carboxylic acid.

de Meijere, A.; Kozhushkov, S.I.; Yufit, D.S.; Grosse, C.; Kaiser, M.; and Raev, V.A., *Beilstein J.Org.Chem.* **10**, 2844 (2014)

## Exercise 95

1– Tetrabutylammonium fluoride, a reagent normally employed for desilylation, is used here as a base. The fluoride anion is a good base because its conjugate acid, hydrofluoric acid, is a weak acid. Thus, the carbanion resulting from deprotonation of the  $\beta$ -ketoester reacts with one of the methyl esters, causing a cyclization and the expulsion of methoxide.



2– Under the basic conditions, a very acidic proton is removed leading to the formation of a carbanion stabilized by three carbonyl groups. This carbanion is methylated by methyl iodide.

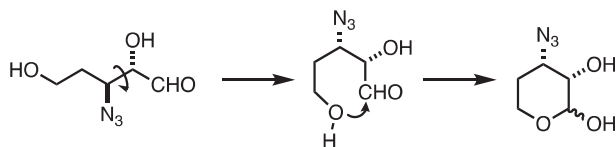
Bulman Page, P.C.; Goodyear, R.L.; Chan, Y.; Slawin, A.M.Z.; and Allin, S.M., *RSC Adv.* **9**, 300019 (2019)

## Exercise 96

1– Trifluoroacetic acid hydrolyses the dimethyl acetal liberating an aldehyde.

2– The fluoride anion in tetrabutylammonium fluoride removes the silyl ether protecting group from the primary alcohol.

3– The primary alcohol adds to the aldehyde producing a stable cyclic hemiacetal as two interchanging anomers.

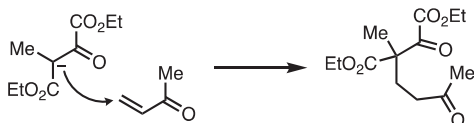


Ong, Q.; Handa, S.; Mete, A.; Hill, A.M.; and Jones, K., *Arkivoc*, **3**, 176 (2002)

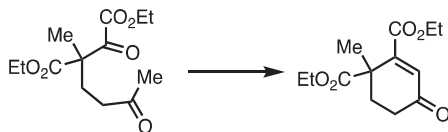
**Exercise 97**

1– The base abstracts a very acidic proton on  $\alpha$  to both the carbonyl groups of the ketone and one of the esters.

2– The resulting anion adds in a conjugated fashion to methyl vinyl ketone.



3– Under the action of piperidine and AcOH, there is an intramolecular aldol condensation between the methyl group on the methyl ketone and the ketone on  $\alpha$  to one of the esters.



Marsden, A.; and Thomas, E.J., *Arkivoc*, **9**, 78 (2002)

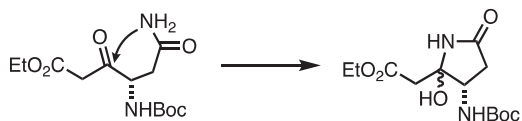
## Exercise 98

1- Reaction of the acid with ethyl chloroformate under basic conditions leads to a mixed anhydride of the kind R-CO-O-CO-OEt.

2- Ammonia reacts with the carbonyl on the left producing the expulsion of CO<sub>2</sub> and ethoxide and the formation of R-CO-NH<sub>2</sub>.



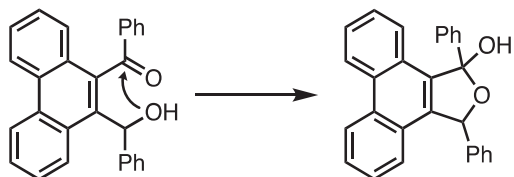
3- The nitrogen in R-CO-NH<sub>2</sub> attacks intramolecularly the ketone leading to a five-membered aminal.



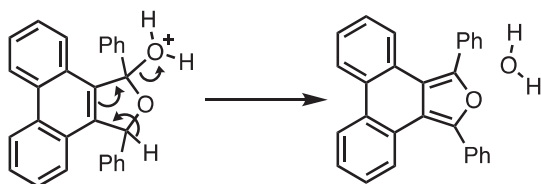
Shioiri, T.; Sasaki, S.; and Hamada, Y., *Arkivoc*, **2**, 103 (2003)

**Exercise 99**

- 1– Sodium borohydride reduces one of the ketones to alcohol.
- 2– The alcohol reacts intramolecularly with the second ketone forming a stable five-membered hemiacetal, thus preventing the reduction of the second ketone.



- 3– The reduction with  $\text{NaBH}_4$  is quenched by addition of  $\text{HCl}$ , that protonates the hydroxy group of the hemiacetal and promotes a dehydration leading to aromatization into an stable furan ring.

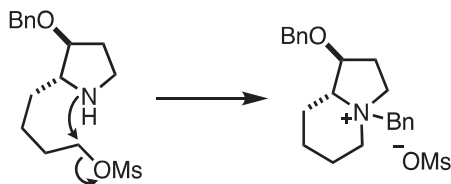


Marchand, A.P.; Srinivas, G.; and Watson, W.H., *Arkivoc*, **3**, 8 (2003)

### Exercise 100

1– Mesyl chloride with triethylamine produces the mesylation of the alcohol.

2– The mesylate alkylates the amine *in situ* yielding an ammonium mesylate.



3– The catalytic hydrogenation debenzylates the alcohol and the ammonium salt.

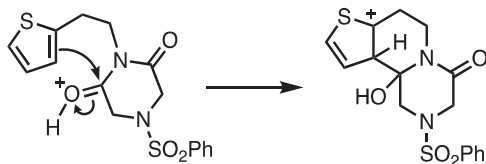
An alternative mechanism involving *N*-debenzylation prior to alkylation of the amine by the mesylate is less likely as suggested by several hints. There are precedents in the literature of similar spontaneous cyclizations to quaternary ammonium salts, and isolation of the mesylate fails during attempted purification by chromatography on silica, probably because of the polar nature of the ammonium salt.

Zheng, J-F.; Chen, W.; Huang, S.-Y.; Ye, J.-L.; and Huang, P.-Q., *Beilstein J.Org.Chem.* **3**, No 41 (2007)

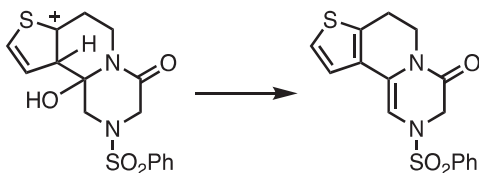


### Exercise 101

1– The thiophene ring attacks a carbonyl group activated by protonation with trifluoromethanesulfonic acid.



2– The thiophene ring recovers the aromaticity by deprotonation, and the aminal is dehydrated to enamine after protonation of the hydroxy group.



3– Loss of phenylsulfonic acid produces the end product. It is important to note that while it is very common in Organic Chemistry to find sulfonates ( $R-SO_3^-$ ) as good-leaving groups, sulfinates ( $R-SO_2^-$ ) are also good-leaving groups.

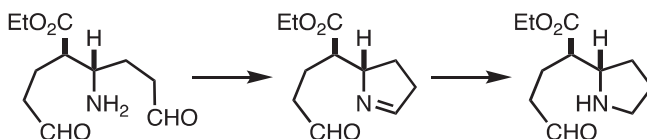
Rao, R.S.; and Ramanathan, C.R., *Beilstein J.Org.Chem.* **13**, 428 (2017)

## Exercise 102

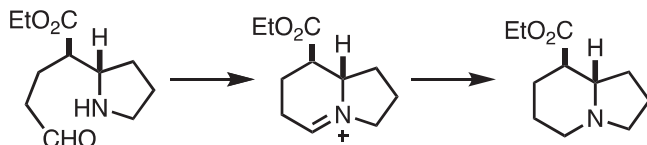
1– Sodium periodate produces an oxidative breakage of the diol resulting in two aldehydes.

2– The catalytic hydrogenation removes the benzyl group giving a carbamic acid. The carbamic acid is transformed in a primary amine with release of carbon dioxide.

3– The primary amine suffers a double reductive alkylation by reaction with both aldehydes under catalytic hydrogenation. This happens stepwise by reaction with one of the aldehydes yielding an imine —or enamine— that is hydrogenated to a secondary amine,



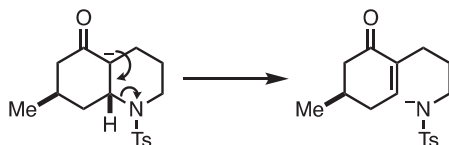
4– The resulting secondary amine reacts similarly with the second aldehyde giving the final product.



Kiss, L.; Forró, E.; and Fülöp, F., *Beilstein J.Org.Chem.* **11**, 596 (2015)

### Exercise 103

- 1– Trifluoroacetic acid removes the *t*-butyl group.
- 2– The resulting acid suffers a very easy decarboxylation because it possesses a keto group at the  $\beta$  position in equilibrium with an enol.
- 3– Lithium hydroxide promotes a retro-aza-Michael reaction via a carbanion on  $\alpha$  to the ketone.

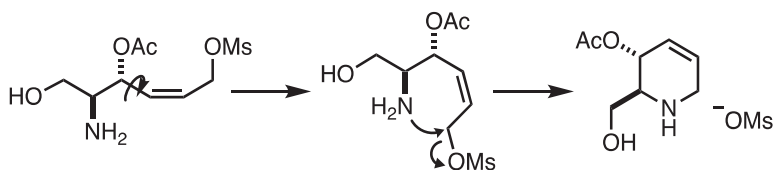


- 4– Benzoylation of the sulfonamide provides the final compound. Potassium iodide is added in order to transform benzyl bromide into benzyl iodide, a better benzylating agent.

Saborit, G.V.; Cativiela, C.; Jiménez, A.I.; Bonjoch, J.; and Bradshaw, B., *Beilstein J.Org.Chem.* **14**, 2597 (2018)

### Exercise 104

- 1– The acidic conditions of the first step produce the deprotection of the isopropylidene and the Boc groups, yielding an amino alcohol where the amine is rendered inactive by protonation.
- 2– Deprotonation of the amine in the second step under  $t$ PrNEt allows an intramolecular *N*-alkylation by reaction with the mesylate producing a piperidine ring.



- 3– Finally, in the third step the amine is protected with Boc anhydride.

Ramalingam, S.; Bhise, A.D.; Show, K.; and Kumar, P., *Arkivoc*, **2**, 220 (2013)

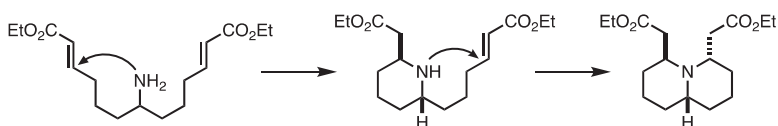
### Exercise 105

The reductive amination of a ketone is followed by a double intramolecular Michael addition.

1– Ammonia condenses with the ketone forming an imine. After trying several desiccants,  $\text{Ti}(\text{OEt})_4$  was found to give satisfactory results.

2– Sodium borohydride reduces the imine to an amine.

3– Heating in acetic acid causes a double addition of the amine to the olefins in the unsaturated esters. Acetone is added to destroy excess of  $\text{NaBH}_4$ .



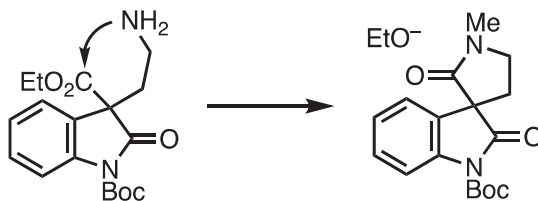
Newton, A.F.; Rejzek, M.; Alcaraz, M-L.; and Stockman, R.A., *Beilstein J.Org.Chem.* **4**, No 4 (2008)

### Exercise 106

1– Methanamine reacts with the aldehyde producing an imine.

2– The imine is reduced to amine by  $\text{NaCNBH}_3$ .

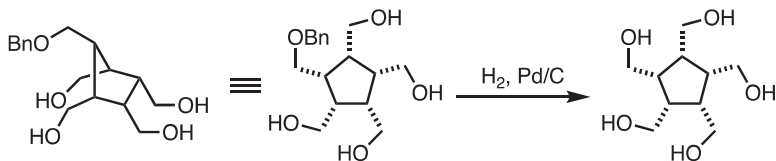
3– The amine reacts with the ester giving a lactame.



Kulkarni, M.G.; Dhondge, A.P.; Chavhan, S.W.; Borhade, A.S.; Shaikh, Y.B.; Birhade, D.R.; Desai, M.P.; and Dhattrak, N.R., *Beilstein J.Org.Chem.* **6**, 876 (2010)

### Exercise 107

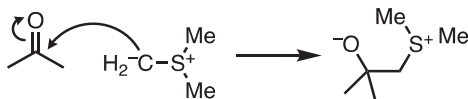
- 1- Ozone reacts with the alkene producing an ozonide.
- 2- Lithium aluminium hydride reduces the ozonide to a diol and the esters to alcohols.
- 3- Catalytic hydrogenation results in debenzoylation of an alcohol giving an interesting pentaol with rotational symmetry of order five.



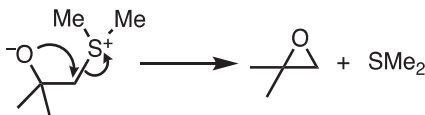
Kelch, A.S., Jones, P.G.; Dix, I.; and Hopf, H., *Beilstein J.Org.Chem.* **9**, 1705 (2013)

### Exercise 108

- 1- The sulfur ylide  $\text{Me}_2\text{S}^+\text{C}-\text{H}_2$  attacks the ketone giving a compound with an alkoxide anion and a sulfonium cation.



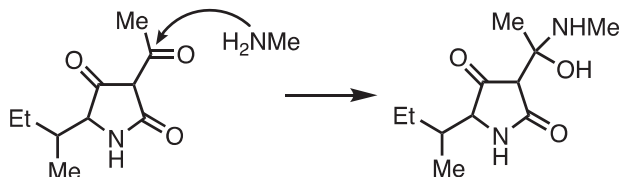
- 2- The alkoxide displaces intramolecularly the sulfur atom, resulting in the formation of an epoxide and the release of  $\text{Me}_2\text{S}$ .



Barbero, A.; Castreño, P.; Pulido, F.J.; Val, P.; González-Ortega, A.; and Sañudo, M.C., *Arkivoc*, **3**, 274 (2010)

**Exercise 109**

- 1- The enol tautomerizes to methyl ketone.
- 2- Methylamine reacts with the methyl ketone forming an iminal.



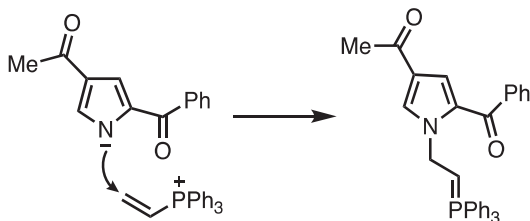
- 3- An anion stabilized by both carbonyls is formed. This anion expels a hydroxy anion leading to the final compound.

Alternatively, methylamine could add in a conjugated manner to the alkene and expel the hydroxy group by an addition-elimination mechanism.

Wang, X.-F.; Si, T.-F.; Li, Q.-B.; Zhu, Z.-Y.; Zhu, X.-J.; Qiang, S.; and Yang, C.-L., *Arkivoc*, **2**, 31 (2010)

**Exercise 110**

- 1-  $\text{NaH}$  abstracts a proton from the nitrogen forming a sodium amide and releasing  $\text{H}_2$ .
- 2- The amide attacks the double bond in  $\text{CH}_2=\text{CHP}^+\text{Ph}_3$  resulting in the formation of a Wittig reagent  $\text{R}_2\text{N}-\text{CH}_2-\text{CH}=\text{PPh}_3$ .



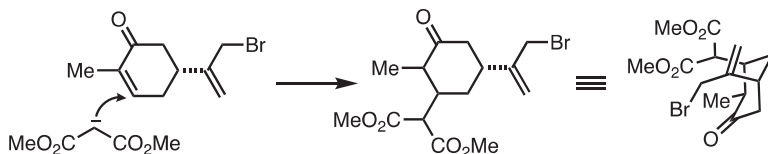
- 3- The Wittig reagent reacts intramolecularly with the neighbouring ketone.

Cantos Llopart, C.; and Joule, J.A., *Arkivoc*, **10**, 20 (2004)

## Exercise 111

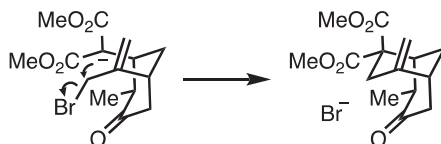
1– The base potassium carbonate generates an anion stabilized by both carbonyls in dimethyl malonate.

2– This anion adds in a conjugated manner to the cyclohexenone.



3– The resulting adduct is deprotonated by  $K_2CO_3$  resulting in the formation of an anion stabilized again by both carbonyls of the malonate moiety.

4– This anion displaces intramolecularly the bromine, giving rise to the second cyclohexane ring.



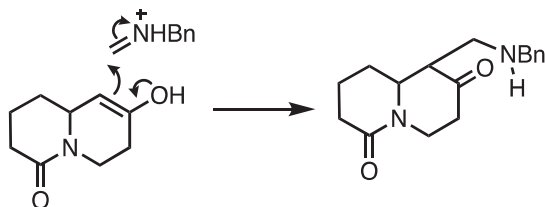
Srikrishna, A.; Kumar, P.P.; and Reddy, T.J., *Arkivoc*, **3**, 55 (2003)

## Exercise 112

A double Mannich condensation of a ketone with benzylamine and formaldehyde yields a 4-piperidone.

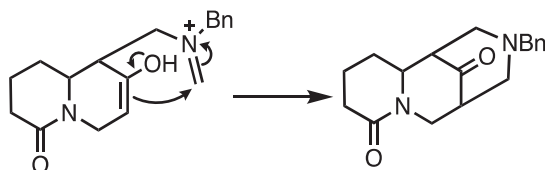
1– The iminium ion  $\text{PhCH}_2\text{N}^+=\text{CH}_2$  is formed by reaction of benzylamine with formaldehyde in equilibrium with paraformaldehyde.

2– The enol tautomer of the ketone is *C*-alkylated by the iminium ion  $\text{PhCH}_2\text{N}^+=\text{CH}_2$ .



3– The resulting amine reacts with formaldehyde yielding a new iminium ion.

4– The new iminium ion reacts intramolecularly with an enol tautomer of the ketone.

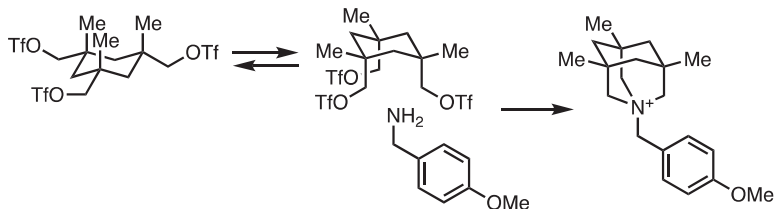


Scheiber, P.; and Nemes, P., *Arkivoc*, **3**, 194 (2008)



### Exercise 113

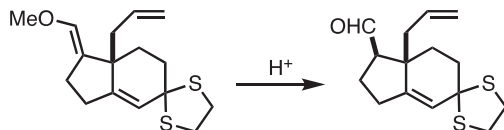
- 1– The alcohols are transformed into the corresponding triflates.
- 2– The conformation of the cyclohexane changes so as to locate the  $\text{TfOCH}_2$ - groups in equatorial position and make possible the alkylation of the amine in *p*-MeOPhCH<sub>2</sub>NH<sub>2</sub> by the three triflates



Izumi, H.; and Futamura, S., *Arkivoc*, **1**, 6 (2000)

### Exercise 114

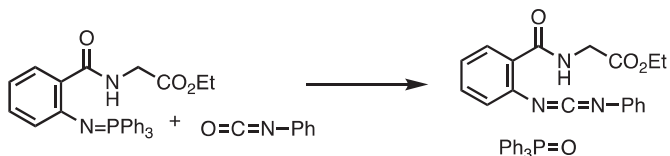
- 1– The Wittig reagent reacts with the ketone producing an enol ether.
- 2– Under acidic conditions, the enol ether hydrolyses to aldehyde.



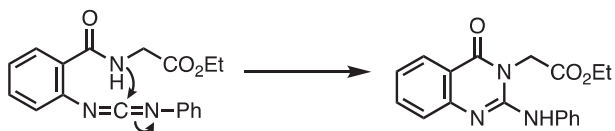
Trzoss, L.; Xu, J.; Lacoske, M.H.; and Theodorakis, E.A., *Beilstein J.Org.Chem.* **9**, 1135 (2013)

### Exercise 115

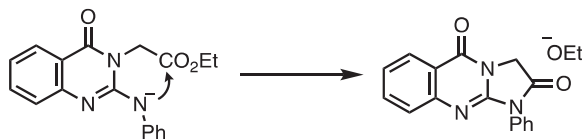
1– The process begins with a so-called aza-Wittig reaction, that is, a modification of the Wittig reaction in which a C=N bond is obtained instead of a C=C bond. The iminophosphorane R-N=PPh<sub>3</sub> reacts with phenyl isocyanate, O=C=N-Ph, yielding a carbodiimide R-N=C=N-Ph and Ph<sub>3</sub>P=O



2– The nitrogen of the amide adds to the very reactive carbodiimide resulting in a six-membered ring being formed.



3– Then sodium ethoxide is added to catalyse the attack of a nitrogen on the ester to form the five-membered ring.



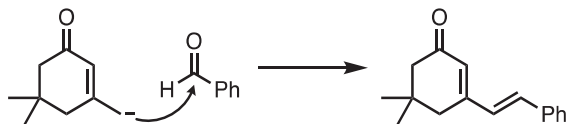
Xie, C; Huang, N.-Y; and Ding, M.-W., *Arkivoc*, **10**, 220 (2009)

## Exercise 116

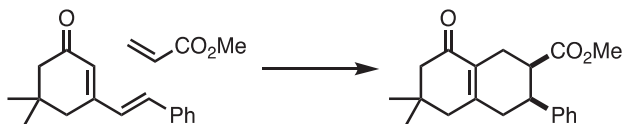
In this one-pot procedure, an aldol condensation at the  $\gamma$  position of an enone is followed *in situ* by a Diels-Alder reaction.

1– A carbanion is formed by  $\gamma$ -deprotonation of the enone under basic conditions.

2– This carbanion condenses with benzaldehyde producing a diene.



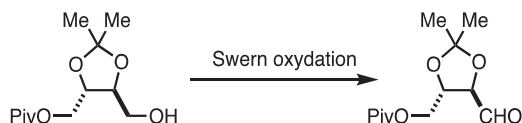
3– The diene reacts with  $\text{CH}_2=\text{CHCO}_2\text{Me}$  in a Diels-Alder reaction.



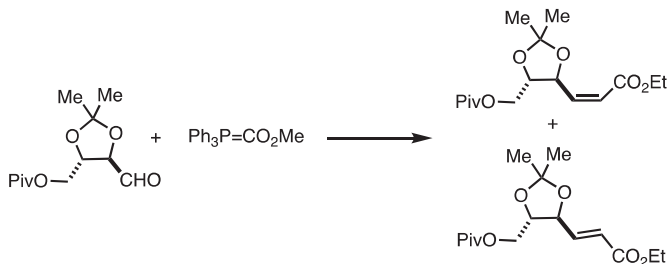
Abae, M.S.; Mobayen, F.; Mojtahedi, M.M.; Saberi, F.; and Khavasi, H.R., *Arkivoc*, 7, 305 (2015)

### Exercise 117

1- The first two operations involve a Swern oxidation of alcohol to aldehyde. Thus, DMSO is activated with oxalyl chloride giving  $\text{Me}_2\text{S}^+\text{Cl}$  that reacts with the alcohol to give  $\text{R-CH}_2\text{-O-S}^+\text{Me}_2$ . This intermediate reacts with triethylamine resulting in the production of  $\text{R-CHO}$  plus dimethylsulfide.



2- The aldehyde reacts with the Wittig reagent  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$  yielding a mixture of (*cis*) and (*trans*)-alkenes with the (*cis*)-alkene being the mayor product.



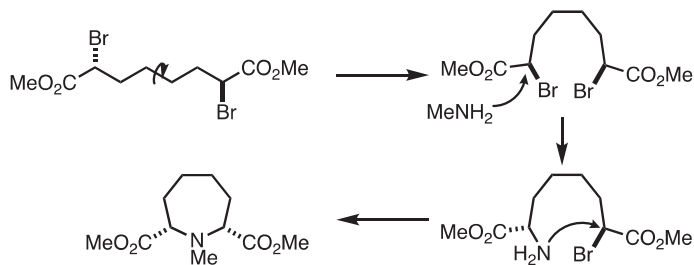
3- The acetal is removed under acidic conditions and the (*cis*) isomer evolves to a lactone, while the (*trans*) isomer is unable to form a lactone because of geometric constraints.



Cucarull-González, J.R.; Alibés, R.; Figueredo, M.; and Font, J., *Arkivoc*, **3**, 193 (2015)

### Exercise 118

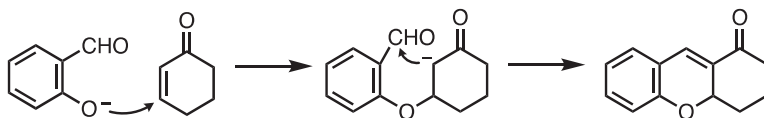
This is a double alkylation of methylamine with a dibromide, where the stereochemistry of the chiral centres in the final seven-membered cycle is dictated by the inversion of stereochemistry in the  $S_N2$  alkylations.



Paliulis, O.; Peters, D.; Holzer, W.; and Šačkus, A., *Arkivoc*, **4**, 240 (2013)

### Exercise 119

Michael addition of phenoxide to cyclohexenone is followed by aldol condensation between the ketone and the aldehyde



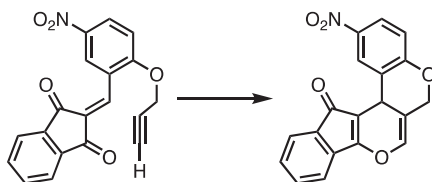
Rodrigues Jr., M.T.; Santos, H.; Zeoly, L.A.; Simoni, D.A.; Moyano, A.; and Coelho, F., *Arkivoc*, **2**, 77 (2020)

## Exercise 120

A Knoevenagel condensation is followed *in situ* by an intramolecular hetero Diels-Alder addition.

1– There is a Knoevenagel condensation between the  $\beta$ -diketone and the aldehyde.

2– This is followed by an intramolecular hetero Diels-Alder reaction between an enone and the alkyne. The alkyne is probably activated by complexation with  $\text{Cu}^+$ .

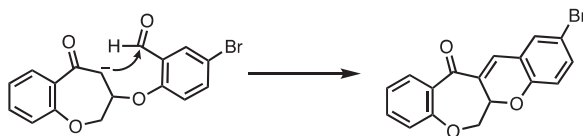


Malihe Javan Khoshkholgh, M.J.; Balalaie, S.; Bijanzadeh, H.R.; and Gross, J.H., *Arkivoc*, 9, 114 (2009)

## Exercise 121

1– The base forms a phenoxide that adds in a conjugated manner to the enone.

2– The ketone condenses intramolecularly with the aldehyde.



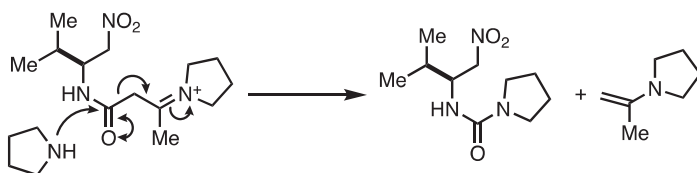
Chen, P.-Y.; Zhon, C.-Y.; Chen, H.-M.; Yang, C.-H.; Wang, T.-P.; and Wang, E.-C., *Arkivoc*, 3, 24 (2013)

## Exercise 122

It was intended to form an enamine by condensation of pyrrolidine with the ketone, but molecules behaved in an unexpected way following a retro-Claisen condensation.

1– Pyrrolidine condenses with the ketone forming an iminium ion in equilibrium with the desired enamine.

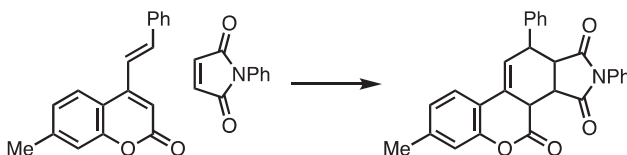
2– Another molecule of pyrrolidine attacks the carbonyl of the amide and expels the enamine that would be obtained by condensing pyrrolidine with acetone



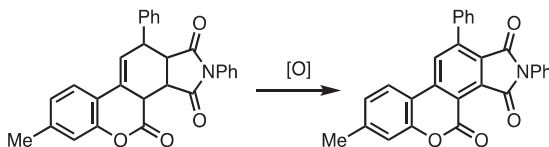
Jones, R. C.F.; Law, C.C.M.; and Elsegood, M.R.J., *Arkivoc*, **3**, 81 (2013)

## Exercise 123

1– There is a Diels-Alder reaction between the diene and *N*-phenylmaleimide.



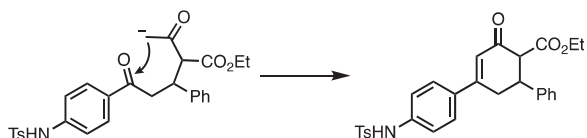
2– DDQ oxidizes the resulting cyclohexene to an aromatic ring.



Sanap, K.K.; and Samant, S.D., *Arkivoc*, **3**, 109 (2013)

## Exercise 124

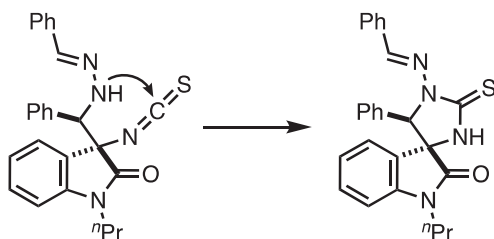
- 1– Potassium carbonate deprotonates ethyl acetylacrylate and the resulting enolate adds in a conjugated fashion to the enone.
- 2– An intramolecular aldol condensation yields the final cyclohexenone.



Agrawal, N.R.; Bahekar, S.P.; Agrawal, A.R.; Sarode, P.B.; and Chandak, H.S., *Arkivoc*, **4**, 227 (2016)

## Exercise 125

- 1– The enol tautomer of the oxindole adds to one of the carbon-nitrogen double bonds of the azine.
- 2– One of the nitrogens of the resultant intermediate attacks intramolecularly the carbon in the isothiocyanate.

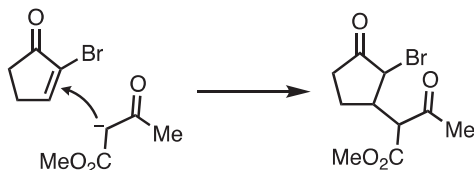


Ping, X.-N.; Chen, W.; Lu, X.-Y.; and Xie, J.-W., *Arkivoc*, **6**, 274 (2016)

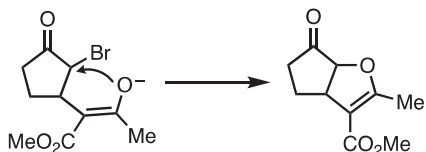


### Exercise 126

1– The enolate of methyl acetylacacetate adds to the alkene in the enone.



2– In the resulting adduct, an enolate is formed on the acetylacacetate portion of the molecule. This enolate is *O*-alkylated intramolecularly by reaction with the bromide.



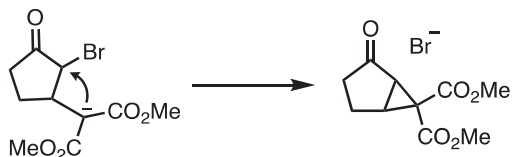
Note: Tetrabutylammonium bromide is used as a phase-transfer catalyst.

Yirsaw, A.M.; and Carlson, R.E., *Arkivoc*, **4**, 74 (2017)

### Exercise 127

1– The enolate of methyl malonate adds to the cyclopentenone.

2– In the resulting adduct, an enolate is formed on the malonate portion of the molecule. This enolate is *C*-alkylated intramolecularly by reaction with the bromide.

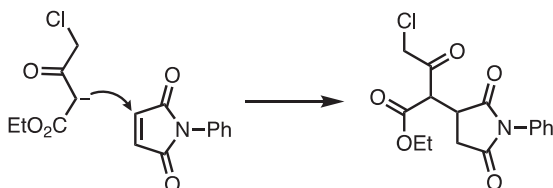


Note:  $\text{BnMe}_2\text{N}(\text{Cl})\text{CH}_2\text{CH}_2\text{OH}$  is used as a phase-transfer catalyst.

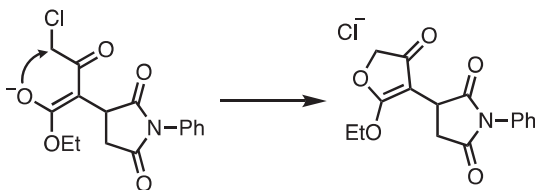
Yirsaw, A.M.; and Carlson, R.E., *Arkivoc*, **4**, 74 (2017)

**Exercise 128**

1– An enolate is formed by deprotonation of an acidic proton located between both carbonyls in ethyl chloroacetylacetate. This enolate is C-alkylated by addition to the alkene in the maleimide.



2– An enolate is formed by deprotonation of the chloroacetylacetate portion of the resulting molecule. This enolate is intramolecularly O-alkylated by reaction with the chloride.



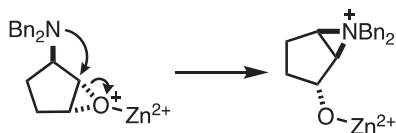
Wang, W.; Liang, G.; Bai, Y.; Bai, L.; Zhou, H.; Yu, Y.; and Zhou, J., *Arkivoc*, **4**, 236 (2017)

## Exercise 129

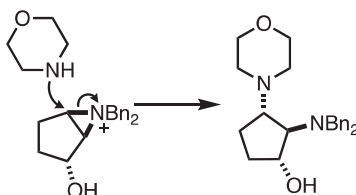
It is quite easy to explain the minor product as the result of opening of the epoxide by attack of morpholine, the zinc cation acting as a Lewis acid to activate the epoxide.

The mayor product results from an unexpected tortuous route:

1– The tertiary amine attacks intramolecularly the activated epoxide resulting in an unstable aziridinium cation.



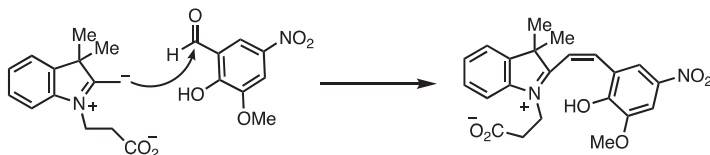
2– Morpholine attacks the aziridinium ring from the less hindered side.



Larin, E.A.; Kochubei, V.S.; and Atroshchenko, Y.M., *Beilstein J.Org.Chem.* **10**, 2513 (2014)

## Exercise 130

1– The base piperidine generates a carbanion stabilized by the iminium cation. The carbanion condenses with the aldehyde.

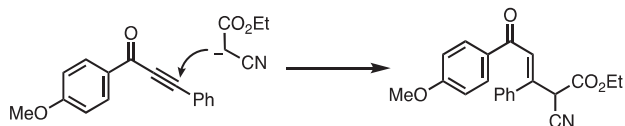


2– A phenoxide is formed that attacks the iminium functional group.

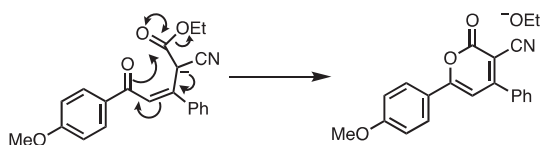
Perry, A.; and Kousseff, C.J., *Beilstein J.Org.Chem.* **13**, 1542 (2017)

### Exercise 131

1– The anion of ethyl cyanoacetate adds in a Michael fashion to the ynone.



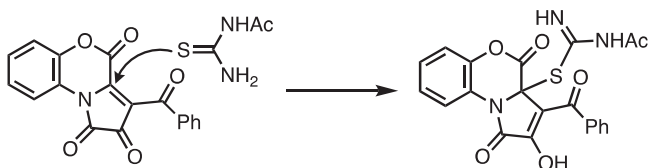
2– Deprotonation at the  $\gamma$  position of the ketone yields a delocalized anion that attacks via oxygen the ester expelling ethoxide.



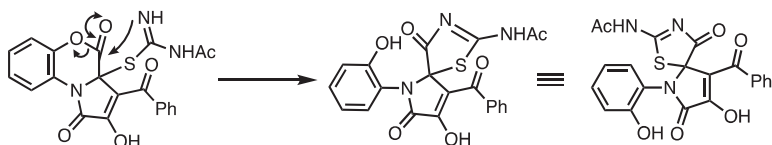
Breuer, N.; Gruber, I.; Janiak, C.; and Müller, T.J.J., *Beilstein J.Org.Chem.* **15**, 2684 (2019)

### Exercise 132

1– The sulfur in thiourea attacks the very activated olefin giving a delocalized anion that is protonated on one oxygen.



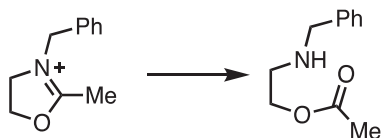
2– One of the nitrogens in the thiourea reacts with the lactone expelling a phenoxide.



Kobelev, A.I.; Tretyakov, N.A.; Stepanova, E.E.; Dmitriev, M.V.; Rubin, M.; and Maslivets, A.N., *Beilstein J.Org.Chem.* **15**, 2864 (2019)

### Exercise 133

1– Benzylation of the nitrogen yields and iminium cation that is hydrolysed to a secondary amine plus an acetate.

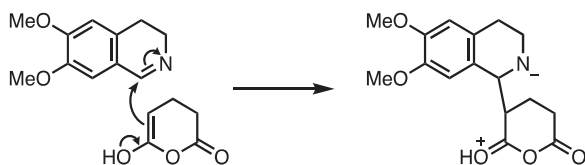


2– The nitrogen is benzylated again.

Lin, Q.; Zhang, S.; and Li, B., *Beilstein J.Org.Chem.* **16**, 492 (2020)

### Exercise 134

1– The enol tautomer of one of the carbonyls in glutaric anhydride attacks the imine.



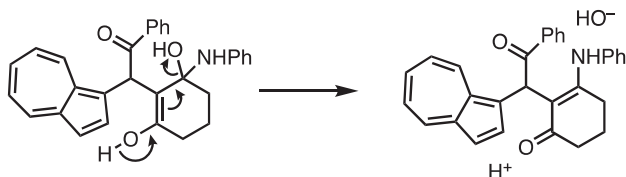
2– After transprotonation, the amine attacks one of the carbonyls of the anhydride, expelling a carboxylic acid.



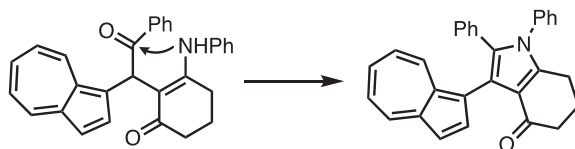
Pashev, A.; Burdzhiev, N.; and Stanoeva, E., *Beilstein J.Org.Chem.* **16**, 1456 (2020)

**Exercise 135**

- 1– Aniline condenses with the ketone giving an aminal.
- 2– The aminal loses water resulting in an aminocyclohexenone.



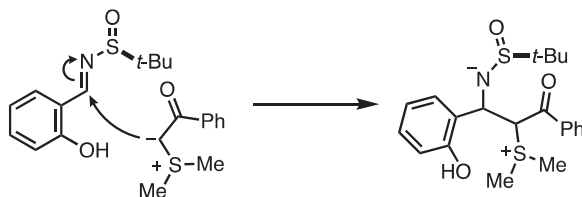
- 3– The amine condenses with the phenyl ketone producing an enamine inside a pyrrole ring.



Gonga, J.; Peshkovb, A.A.; Yua, J.; Amandykovab, S.; Gimnkhanb, A.; Huang, J.; Kashtanovc, S.; Pereshivko, O.P.; and Peshkov, V.A., *RSC Adv.* **10**, 10113 (2020)

**Exercise 136**

- 1– Potassium carbonate takes a proton from the sulfonium salt, forming a sulfur ylide that attacks the imine.

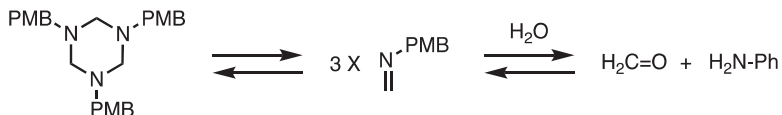


- 2– After transprotonation phenoxide displaces the sulfonium salt.

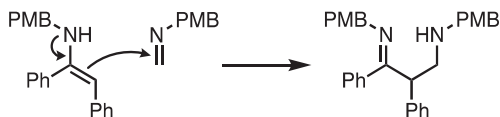
Zhang, M.; Lu, T.; Zhao, Y.; Xie, G.; and Miao, Z., *RSC Adv.* **9**, 11978 (2019)

### Exercise 137

The triazine operates as a source of both  $p\text{-MeOPh-N=CH}_2$  and formaldehyde by the following equilibria:



1– The imine tautomerizes to the corresponding enamine that adds to  $p\text{-MeO-Ph-N=CH}_2$ .

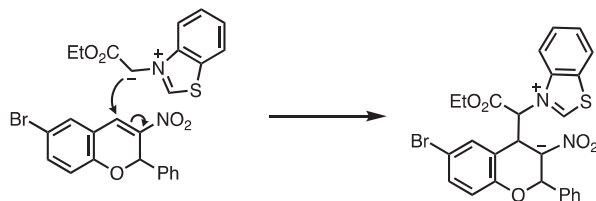


2– After isomerization to enamine, both nitrogens condense with formaldehyde.

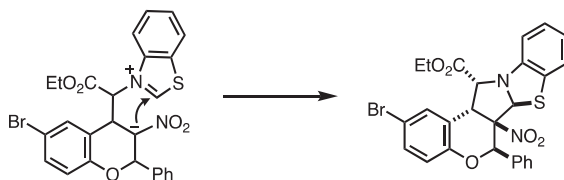
Chen, L.; Liu, K.; and Sun, J., *RSC Adv.* **8**, 5532 (2018)

**Exercise 138**

1– Triethylamine forms a carbocation stabilized by the ester. This carbocation adds to the nitroolefin.



2– The resulting anion on  $\alpha$  to the nitro group reacts with the iminium salt.

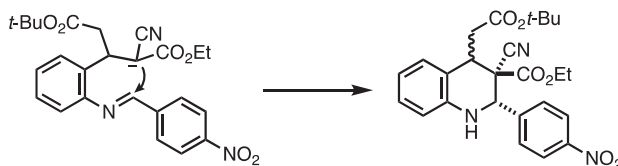


Jiang, W.; Sun, J.; and Yan, C.-G., *RSC Adv.*, **7**, 42387 (2017)

**Exercise 139**

1– The enolate formed by deprotonation of ethyl cyanoacetate by DBU performs a conjugate addition on the unsaturated ester.

2– DBU deprotonates the acidic proton on  $\alpha$  to the ester and cyano groups and the resulting carbanion attacks intramolecularly the imine.

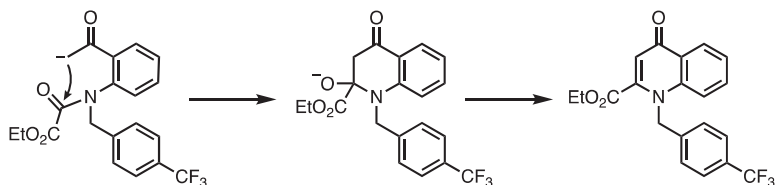


Palanimuthu, A.; Chen, C.; and Lee, G.-H., *RSC Adv.*, **10**, 13591 (2020)



### Exercise 140

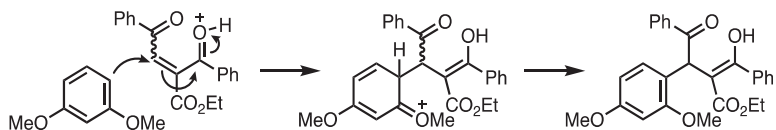
- 1– The amine reacts with diethyl oxalate generating an amide.
- 2– The strong base LHMDS abstracts a proton from the methyl ketone and the resulting anion attacks the carbonyl of the amide, yielding the final product after removal of water.



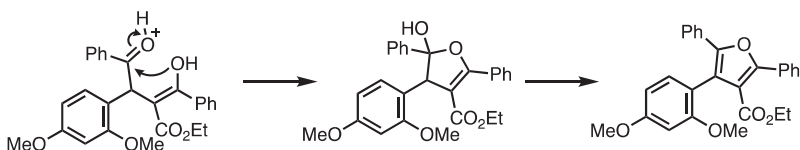
Hasan, P.; Aneja, B.; Masood, M.M.; Ahmad, M.B.; Yadava, U.; Daniliuc, C.G.; and Abid, M., *RSC Adv.*, 7, 11367 (2017)

### Exercise 141

- 1– The first step is a Friedel-Crafts alkylation with an electron-poor olefin operating as electrophile. The aromatic ring attacks —via its less hindered and more electron-rich position— the protonated diketoester.



- 2– The oxygen atom of the resulting enol attacks the protonated ketone yielding the final product after dehydration.

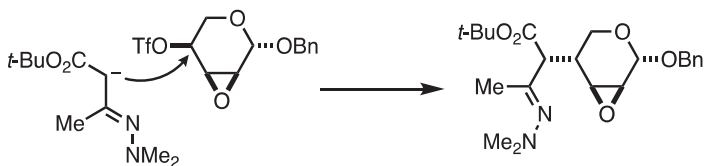


## Exercise 142

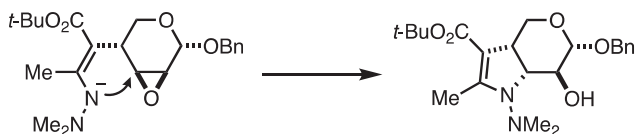
This is a case of a ring formation by double alkylation of a double nucleophile by a double electrophile.

1– Sodium hydride abstracts a very acidic proton on  $\alpha$  to the *t*-butyl ester, resulting in an anion stabilized by de carbonyl and the hydrazone.

2– This anion is C-alkylated by displacement of the triflate.



3– Sodium hydride abstracts a second hydrogen on  $\alpha$  to the *t*-butyl ester, resulting in a polydentate nucleophile that reacts via nitrogen producing the opening of the epoxide.



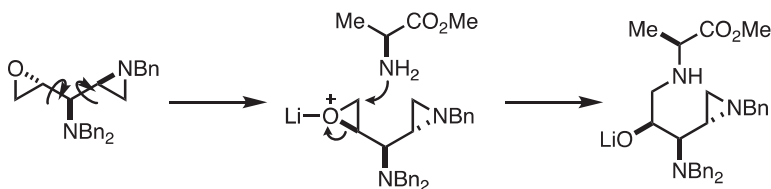
Al-Qawasmeh, R.A.; Al-Telb, T.H.; Khanb, K.M.; Perveen, S.; and Voeltera, W., *Arkivoc* 7, 310 (2007)

### Exercise 143

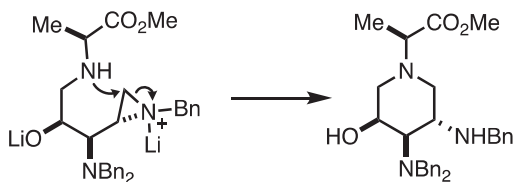
There is a piperidine formation by a double alkylation of an amine with an epoxide and an aziridine. Potassium carbonate is used to liberate the primary amine from its hydrochloride and the lithium cation in  $\text{LiClO}_4$  serves to activate the epoxide and the aziridine by complexation.

1– The amine in the  $\alpha$ -amino acid derivative is liberated from its hydrochloride by sodium bicarbonate.

2– This amine attacks the epoxide that has been previously activated by complexation with  $\text{Li}^+$ . The stereochemistry of the resulting alcohol is dictated by the configuration of the epoxide.



3– The amine reacts intramolecularly with the aziridine activated with  $\text{Li}^+$ . Similarly to above, the stereochemistry of the resulting *N*-dibenzylamino group is dictated by the configuration of the aziridine.

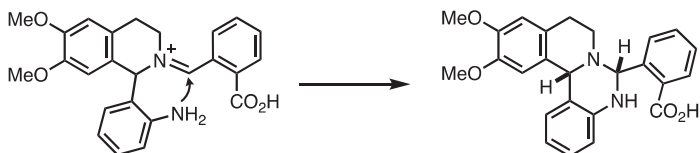


Ochoa-Terán, A.; Concellón, J.M.; and Rivero, I.A., *Arkivoc*, **2**, 288 (2009)

## Exercise 144

1– The amine in the isoquinoline condenses with the aldehyde forming an iminium ion.

2– The second amine condenses with the iminium ion resulting in a six-membered cycle.

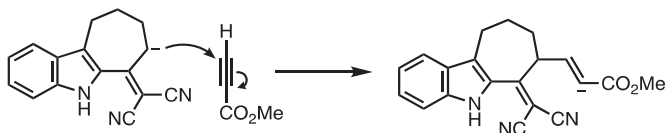


3– Finally, a lactone is formed by condensation of the secondary amine with the carboxylic acid.

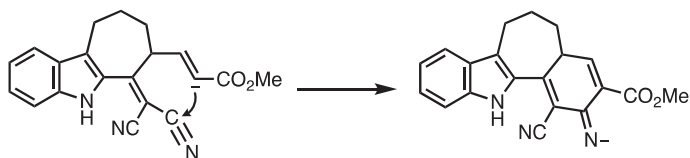
Kivelä, H.; Martiskainen, O.; Pihlaja, K.; Zalán, Z.; and Lázár, L., *Arkivoc*, **5**, 244 (2012)

### Exercise 145

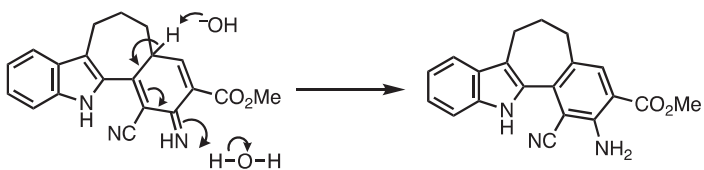
1– Hydroxide abstracts a proton on  $\gamma$  to both cyanides giving an anion that attacks the  $\beta$  position of methyl propiolate.



2– The resulting anion attacks one of the cyanide groups producing a species  $R_2C=N^-$  that is protonated on the nitrogen.



3– The resulting intermediate evolves by deprotonation-protonation to the final aromatic compound.

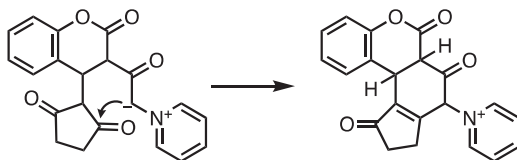


Yamuna, E.; Zellerb, M.; Adero, P.O.; and Rajendra Prasad, K.J., *Arkivoc*, **6**, 326 (2012)

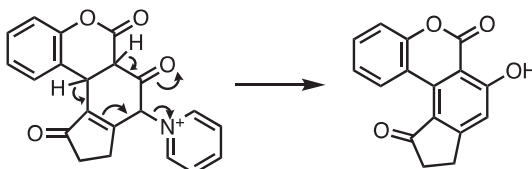
## Exercise 146

1– The enolate of 1,3-cyclopentandione adds to the conjugated olefin in the chromenone molecule.

2– The enolate of the  $\alpha$ -pyridinium ketone reacts with one of the ketones in the 1,3-diketone and the resulting  $\beta$ -hydroxyketone suffers dehydration to an enone.



3– Enolization of one ketone and elimination of pyridine leads to aromatization of the cyclohexane.



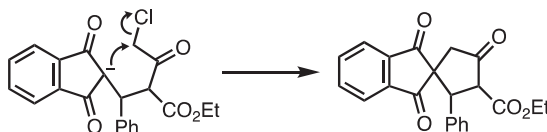
P. Patel, K.P., *Arkivoc*, **3**, 14 (2013)

## Exercise 147

1– Triethylamine abstracts a proton from the 3-oxobutanoate forming the corresponding enolate.

2– The enolate adds in a Michel reaction to the endione, leading to the enolate of a 1,3-diketone.

3- This enolate displaces the chlorine.

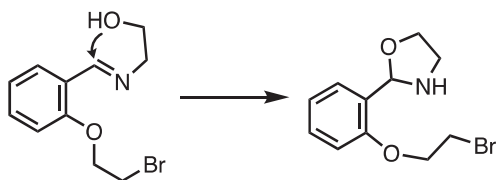


Luo, N.-H.; Zheng, D.-G.; Zhang, X.-J.; and Yan, M., *Arkivoc*, **5**, 383 (2015)

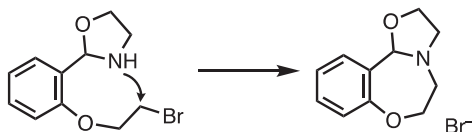
### Exercise 148

1– Condensation between the amine and the aldehyde yields an imine.

2– Intramolecular attack of the alcohol on the imine produces a five-membered hemiaminal ether.



3– Displacement of the bromine by attack of the nitrogen in the hemiaminal ether results in the formation of the seven-membered ring.

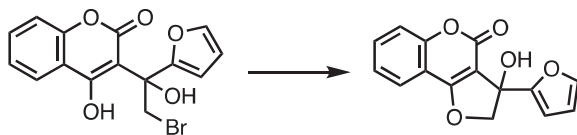


Ashram, M.; and Awwadi, F.F., *Arkivoc*, **5**, 142 (2019)

### Exercise 149

1– C-Alkylation of the enol with the ketone gives a  $\beta$ -bromoalcohol.

2– The resulting ketone tautomerizes to enol and the oxygen of the enol displaces the bromine giving a dihydrofuran.



3– The dihydrofuran is aromatized by dehydration.

Patel, M.; Parikh, P.; Timaniya, J.; and Patel, K., *Arkivoc*, **6**, 155 (2020)

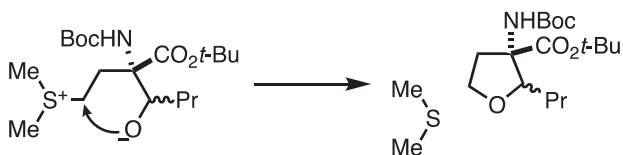
### Exercise 150

1– The base CsOH generates an enolate by abstracting a proton on  $\alpha$  to the carbonyl of the ester.

2– The enolate is C-alkylated by reaction with the aldehyde resulting in an alkoxide.



3– The alkoxide reacts intramolecularly via an  $S_N2$  reaction where the sulfur in the sulfonium salt functions as a leaving group.

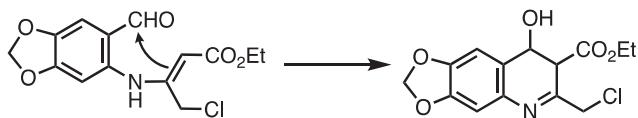


Grauer, A.A.; and König, B., *Beilstein J.Org.Chem.* **5**, No 5 (2009)

### Exercise 151

1– The amine condenses with the ketone yielding an enamine.

2– The enamine attacks the aldehyde providing an alcohol.



3– Dehydration of the alcohol gives the final aromatic compound.

Gao, W.; Liu, J.; Jiang, Y.; and Li, Y., *Beilstein J.Org.Chem.* **7**, 210 (2011)

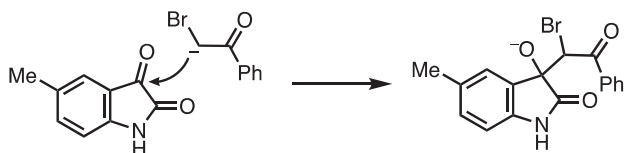


## Exercise 152

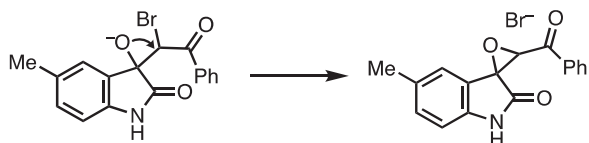
This is modification of the so-called Darzens reaction in which an epoxide is prepared by condensation between an  $\alpha$ -haloester and a ketone or aldehyde. In this modification, an  $\alpha$ -haloketone is used in place of an  $\alpha$ -haloester.

1– The base transforms the  $\alpha$ -bromoketone into the corresponding enolate.

2– The enolate reacts with the ketone in the isatin.



3– This results in the formation of an alkoxide that displaces the bromine.

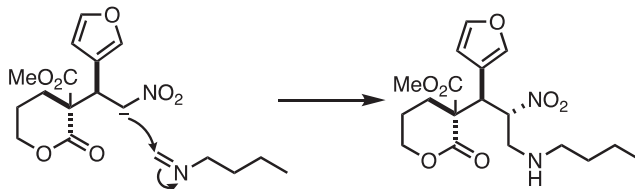


Fu, Q.; and Yan, C.-G., *Beilstein J.Org.Chem.* **9**, 918 (2013)

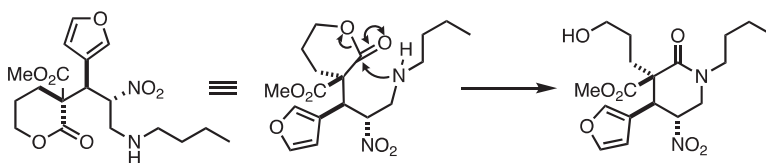
### Exercise 153

There is a nitro-Mannich reaction followed by lactamisation.

- 1– Butanamine condenses with formaldehyde forming an imine.
- 2– The nitro compound reacts with the imine.



- 3– The resulting amine forms a lactam by nucleophilic attack on the lactone.

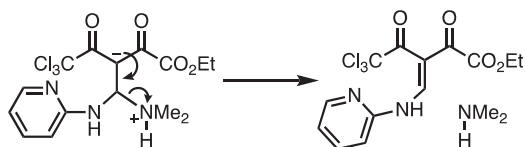


Jakubec, P.; Farley, A.J.M.; and Dixon, D.J., *Beilstein J.Org.Chem.* **12**, 1096 (2016)

## Exercise 154

1– The amine in the aminopyridine makes a conjugated addition to the carbon-carbon double bond.

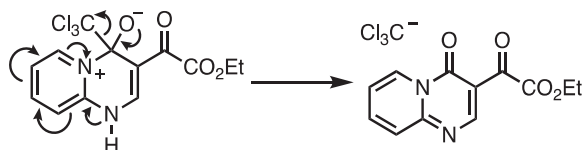
2– The addition is followed by elimination of dimethylamine after protonation.



3– The nitrogen inside the pyridine ring attacks the ketone.



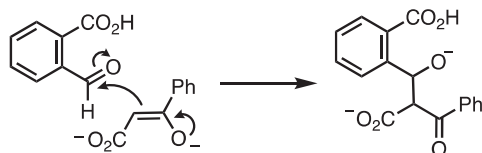
4– Deprotonation of one of the nitrogens and expulsion of  $\text{Cl}_3\text{C}^-$  yields the ultimate molecule. It is important to note that the trichloromethyl anion is lost easily because it is stable due to the electron-withdrawing properties of the three very electronegative chlorine atoms.



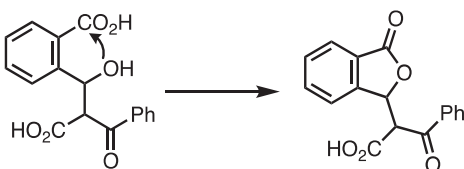
Campos, P.T.; Rodrigues, L.V.; Belladonna, A.L.; Bender, C.R.; Bitencurt, J.S.; Rosa, F.A.; Back, D.F.; Bonacorso, H.G.; Zanatta, N.; Frizzo, C.P.; and Martins, M.A.P., *Beilstein J.Org.Chem.* **13**, 257 (2017)

## Exercise 155

1– Double deprotonation of the ketoacid gives a dianion that condenses via enolate with the aldehyde.



2– The alkoxide and the carboxylate are protonated, and the alcohol condenses with one of the carboxylic acids to form a lactone.



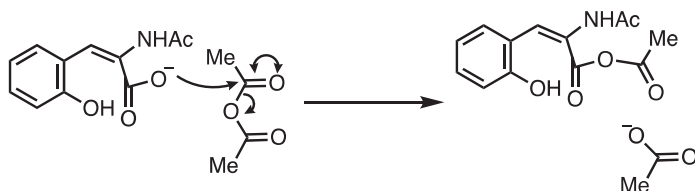
3– Finally, the carboxylate on the  $\alpha$ -position of the ketone suffers an easy decarboxylation promoted by a favourable release of  $\text{CO}_2$  and the obtainment of a carbanion stabilised by a ketone.

Jia, L.; and Han, F., *Beilstein J.Org.Chem.* **13**, 1425 (2017)

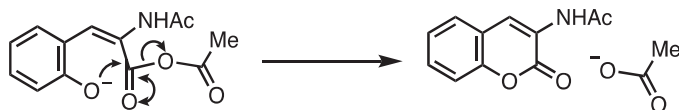
### Exercise 156

1– *N*-Acetylglycine condenses with the aldehyde.

2– The carboxylic acid reacts with acetic anhydride producing a mixed anhydride.



3– The phenol reacts with the mixed anhydride expelling acetate.

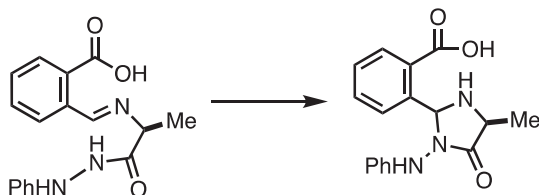


Khunnawutmanotham, N.; Laongthipparos, C.; Saparpakorn, P.; Chimnoi, N.; and Techasakul, S., *Beilstein J.Org.Chem.* **14**, 2545 (2018)

### Exercise 157

1– The amine condenses with the aldehyde to form an imine.

2– One of the nitrogens of the acylhydrazine reacts with the imine resulting in an aminal.

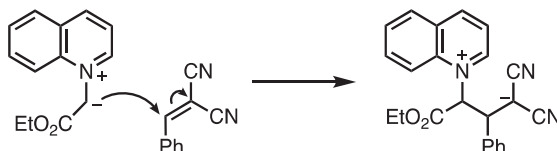


3– One of the nitrogens of the aminal condenses with the carboxylic acid giving a lactam.

Bouzayani, N.; Kraïem, J.; Marque, S.; Kacem, Y.; Carlin-Sinclair, A.; Marrot, J.; and Hassine, B.B., *Beilstein J.Org.Chem.* **14**, 2923 (2018)

**Exercise 158**

- 1– Triethylamine abstracts a proton leading to a nitrogen ylide.
- 2– The carbanion in the nitrogen ylide performs a Michael addition on the olefin activated by conjugation with two nitriles.

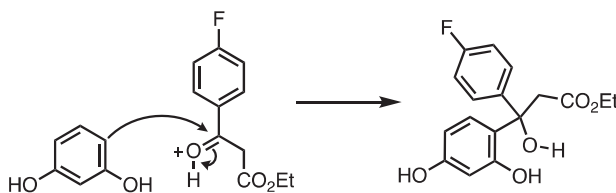


- 3– The carbanion stabilised by two nitriles adds to the iminium group.

Choi, A.; Morley, R.M.; and Coldham, I., *Beilstein J.Org.Chem.* **15**, 1480 (2019)

**Exercise 159**

- 1– There is a Friedel-Crafts alkylation by attack of a very electron-rich arene on a protonated ketone.



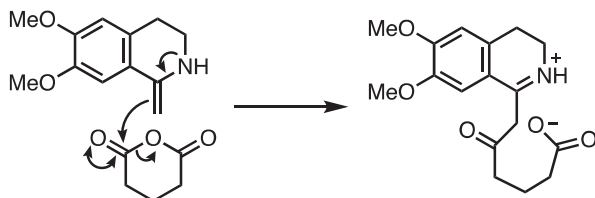
- 2– The alcohol is dehydrated under acid catalysis.
- 3– One phenol attacks the carbonyl of the ester expelling ethanol and yielding a lactone.

Mzozoyana, V.; van Heerden, F.R.; and Grimmer, C., *Beilstein J.Org.Chem.* **16**, 190 (2020)

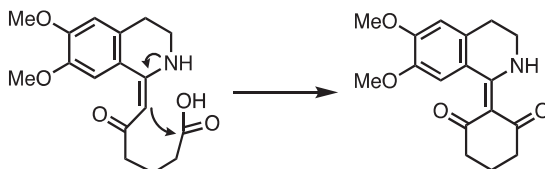
**Exercise 160**

1– The imine tautomerizes to an enamine with an exocyclic alkene that is very nucleophilic.

2– This alkene attacks one of the carbonyls in glutaric anhydride expelling a carboxylate.



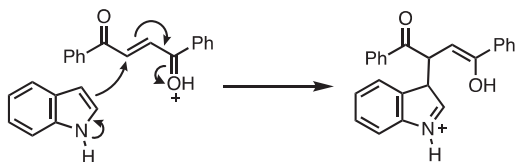
3– After transprotonation, the resulting imine tautomerizes again to enamine and the alkene attacks the carbonyl of the carboxylic acid expelling hydroxide.



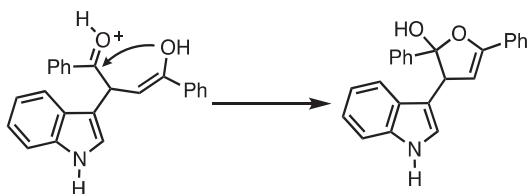
Pashev, A.; Burdzhiev, N.; and Stanoeva, E., *Beilstein J.Org.Chem.* **16**, 1456 (2020)

## Exercise 161

1– Indole attacks the olefin, which is activated by protonation of a ketone it is conjugated with.



2– After rearomatization of the indole, the resulting enol attacks intramolecularly the protonated ketone.



3– Acid-catalysed dehydration of the resulting hemiacetal delivers the end product.

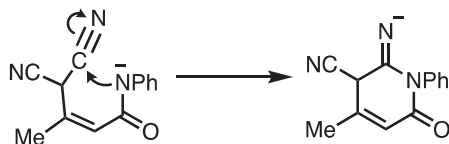
Chatterjee, S.; Bhattacharjee, P.; Butterfoss, G.L.; Achari, A.; Jaisankar, P., *RSC Adv.* **9**, 22384 (2019)



### Exercise 162

1– Malononitrile condenses with the ketone and the intermediate alcohol is dehydrated to form an alkene conjugated with the amide.

2– Deprotonation of the nitrogen in the amide leads to an anion that attacks one of the cyanides.



3– Protonation of the resulting imine anion and tautomerization produces the final product.

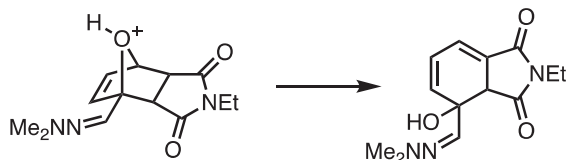
Gao, B.; Sun, Y.; Wang, J.; Yuan, Z.; Zu, L.; Zhang, X.; and Liu, W., *RSC Adv.* **8**, 33625 (2018)

### Exercise 163

[bmim][Cl] consists in 1-butyl-3-methylimidazolium chloride, an ionic liquid used as solvent that facilitates de elaboration. Heating is carried out by microwave irradiation because it delivers a better yield.

1– There is a Diels-Alder addition in which the furane operates as the diene and the pyrroledione as dienophile.

2– The ether inside the resulting bicyclic adduct suffers elimination after protonation by adventitious water.

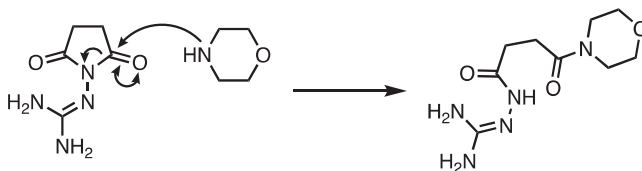


3– This produces an alcohol that delivers the final aromatic compound by dehydration.

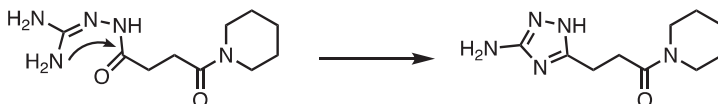
Karaluka, V.; Murata, K.; Masuda, S.; Shiramatsu, Y.; Kawamoto, T.; Hailes, H.C.; Sheppard, T.D.; and Kamimura, A., *RSC Adv.* **8**, 22617 (2018)

## Exercise 164

1– Morpholine reacts with one of the carbonyl groups and expels a nitrogen.



2– One of the nitrogen atoms in the guanidine moiety condenses with the proximal carbonyl group.

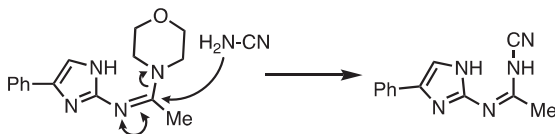


3– Finally, tautomerization gives rise to the product.

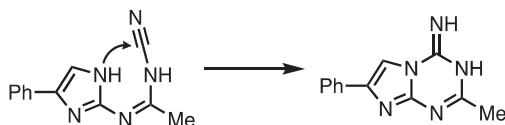
Phei Lin Lim, F.; Yuing Tan, L.; Tiekink, E.R.T.; and Dolzhenko, A.V., *RSC Adv.* **8**, 22351 (2018)

**Exercise 165**

1– The  $\text{-NH}_2$  group in cyanamide attacks the  $\text{C}=\text{N}$  bond in the amidine moiety and expels the morpholine.



2– One of the nitrogen atoms in the imidazole attacks the cyano group.



3– The compound resulting from the previous step tautomerizes to the final product.

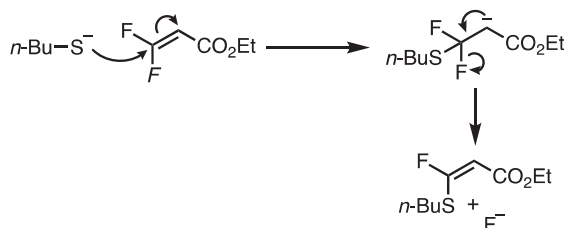
Phei Lin Lim, F.; Yuing Tan, L.; Tiekinkb, E.R.T.; and Anton V. Dolzhenko, A.V., *RSC Adv.* **8**, 21495 (2018)

## Exercise 166

Fluoride is a very bad leaving-group due to the very low stability of the  $F^-$  anion as reflected by the minimal acidity of hydrofluoric acid ( $pK_a = 3.1$ ). This reaction illustrates how it is possible to overcome the negligible nucleofugicity of fluoride using a powerful nucleophile –a thiolate– enhanced with a voluminous and stable caesium cation that leaves a naked very reactive counter anion.

1– Caesium carbonate induces de elimination of hydrofluoric acid leaving a exceedingly electron-poor alkene very prone to nucleophilic attacks.

2– The alkene undergo the attack of *n*-butylthiolate leading to an anionic intermediate that evolves by ejection of fluoride.

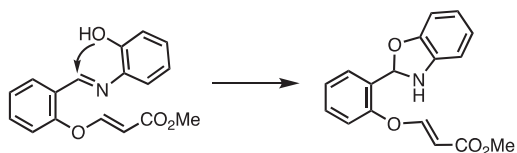


3– An analogous mechanisms leads to the replacement of a second fluoride by sulfur.

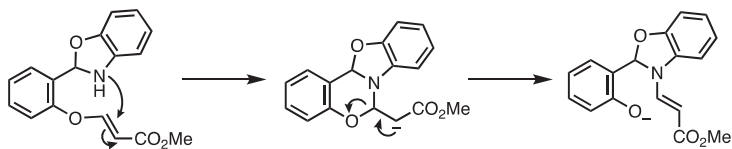
Wu, Y.; Zhang, B.; Zheng, Y.; Wang, Y.; and Lei, X., *RSC Adv.* **8**, 16019 (2018)

**Exercise 167**

- 1– An imine is formed by condensation of the amine with the aldehyde.
- 2– Intramolecular attack of the phenol on the imine prompts the generation of an oxazole.



- 3– Aza-Michael addition of the nitrogen on the unsaturated ester furnishes an anion that evolves to the final compound by a retro aza-Michael reaction followed by protonation of the phenoxide.

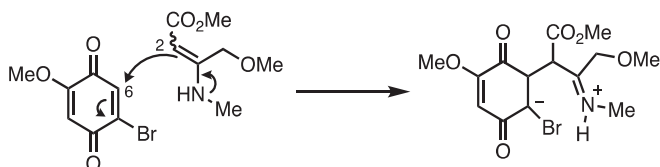


Bakthadoss, M.; and Mushaf, M. *RSC Adv.* **8**, 12152 (2018)

## Exercise 168

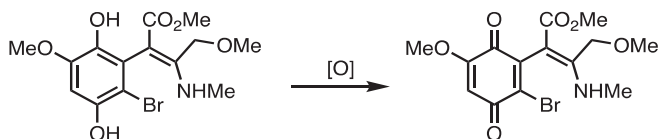
This fascinating indole synthesis involves the conjugate addition of an enamine via carbon to a very electron-poor alkene in a quinone, leading to a hydroquinone that is transformed back to quinone by aerial oxidation. Then, the bromine in the new quinone is displaced by the nitrogen in the enamine by a conjugate addition-elimination.

1– The carbon at C-2 of the enamine is electron-rich and functions naturally as a nucleophile that attacks C-6 in the quinone. Both alkenes in the quinone are electron-poor but the alkene on the right is a better electrophile due to the strongly withdrawing effect of the very electronegative bromine atom.



2– The resulting anion is protonated giving a intermediate that evolves to an aromatic hydroquinone. The iminium cation evolves to an enamine

3– The hydroquinone suffers aerial oxidation to the corresponding quinone.



4– The nitrogen in the enamine displaces intramolecularly the bromine by an addition-elimination mechanism.

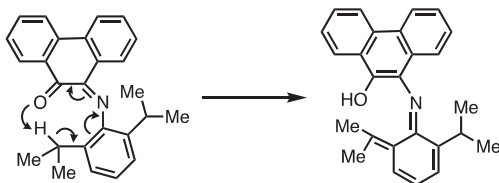
Comer, E.; and Murphy, W.S., *Arkivoc*, 7, 286 (2003)

## Exercise 169

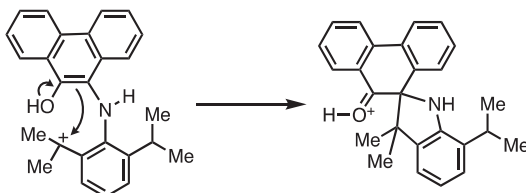
An unexpected spirocompound is formed during an attempted condensation between a ketone and a very hindered amine under forcing conditions.

1– The process begins with the expected condensation of the amine with one ketone resulting in the formation of a very crowded imine.

2– There is a 1,7-shift of a hydrogen from an isopropyl to a ketone.



3– Protonation of the nitrogen is followed by intramolecular C-alkylation of the phenol by a benzyl cation

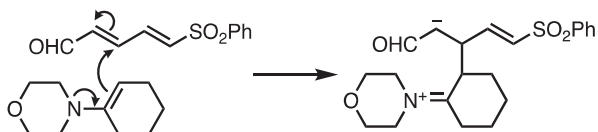


4– Deprotonation of the ketone yields the final spirocompound.

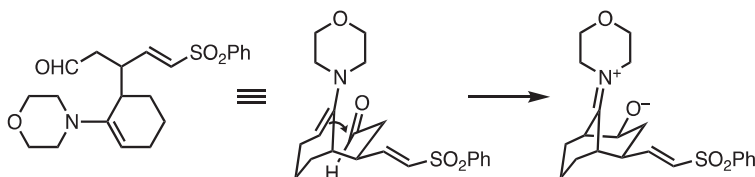
Li, L.; Gomes, C.S.B.; Gomes, P.T. Veiros, L.F.; and Kimb, S.Y., *Arkivoc*, 2, 95 (2009)

**Exercise 170**

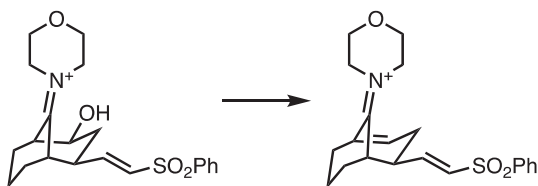
1– The enamine adds in a conjugated manner to the enal.



2– After protonation of the resulting carbocation and transformation of the iminium salt into enamine, the enamine condenses with the aldehyde.



3– After protonation of the alkoxide, the resulting alcohol suffers dehydration probably through an  $E_{1c}B$  mechanism.



4– During work-up, the iminium salt is hydrolysed to an enone and morpholine. Finally, morpholine adds in a conjugated way to the enone.

Note: 2,6-di-*t*-butyl-4-methylphenol is a common antioxidant that prevents radical-induced side reactions.

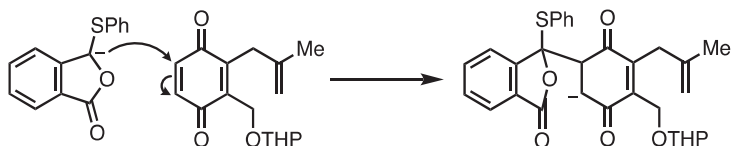
Díez, D.; Sanfeliciano, S.G.; Peña, J.; Flores, M.F.; García, P.; Garrido, N.M.; Marcos, I.S.; White, A.J.; Basabe, P.; and Urones, J.G., *Arkivoc*, **3**, 6 (2011)



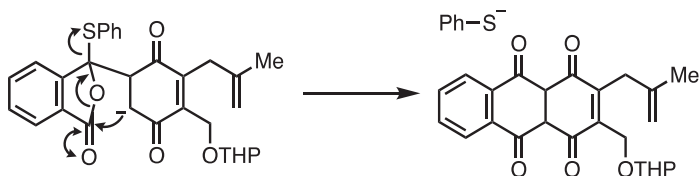
### Exercise 171

1– Lithium *tert*-butoxyde generates an anion at the benzylic position of the molecule on the left. This anion is stabilized on account of several factors: inductive effect of sulfur and oxygen, delocalization on the aromatic ring and extended conjugation with the carbonyl group.

2– This carbanion adds to one of the olefins of the quinone.



3– The carbanion resulting from the previous step adds to the carbonyl of the lactone and through an addition-elimination mechanism expels oxygen with a negative charge. This oxygen evolves by forming a ketone and expelling a sulfide anion.



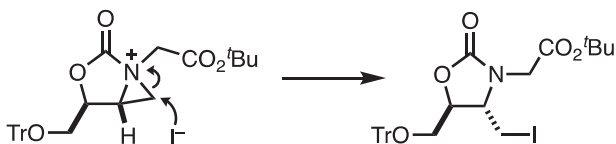
4– Finally, tautomerization of two of the ketones to enol yield an aromatic ring.

Basak, S.; Ray, S.; and Mal, D., *Arkivoc*, **3**, 257 (2018)

## Exercise 172

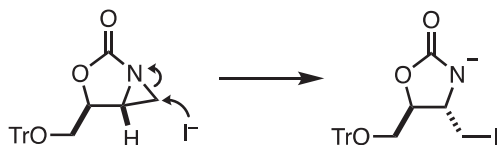
1– The nitrogen is alkylated by reaction with *tert*-butyl iodoacetate resulting in the formation of a positively charged nitrogen atom that is a good-leaving group and the release of iodide anion.

2– The iodide anion attacks a carbon of the aziridine ring in an  $S_N2$  reaction where the positively charged nitrogen functions as a good-leaving group.



There is an alternative mechanistic proposal where bonds are formed in reverse order:

1– The iodide anion attacks one carbon of the aziridine with in an  $S_N2$  reaction where the uretane nitrogen functions as a good-leaving group.



2– This nitrogen is alkylated by *tert*-butyl iodoacetate.

The yield increases to 83% when NaI is added, a fact that supports the second mechanism,

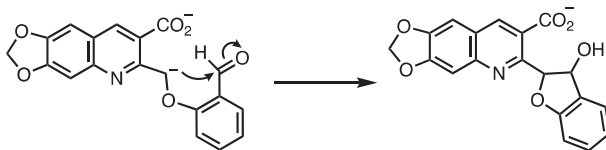
Zheng, Z.; and Bergmeier, S.C., *Arkivoc*, **3**, 40 (2019)

### Exercise 173

1– Treatment with  $K_2CO_3$  leads to a Williamson reaction with formation of an ether by reaction of the phenol with the chloride.

2– KOH produces the hydrolysis of the ester.

3– Additionally, KOH generates an anion at the benzylic position that attacks the neighbouring aldehyde.

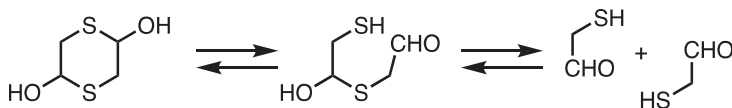


4– The alcohol suffers dehydration to the product.

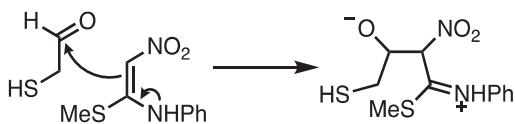
Gao, W.; Liu, J.; Jiang, Y.; and Li, Y., *Beilstein J.Org.Chem.* 7, 210 (2011)

**Exercise 174**

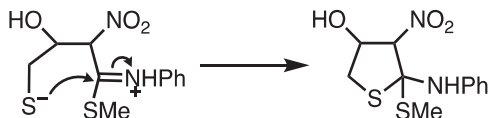
1– The dithiane contains two hemithioacetal units that equilibrate with thiol and aldehyde. In fact, via a two-fold equilibration, the dithiane is a dimer of HS-CH<sub>2</sub>-CHO.



2– The enamine in the compound on the left attacks via carbon the aldehyde in the monomer HS-CH<sub>2</sub>-CHO.



3– Under basic conditions, a thiolate is formed that attacks the iminium cation.



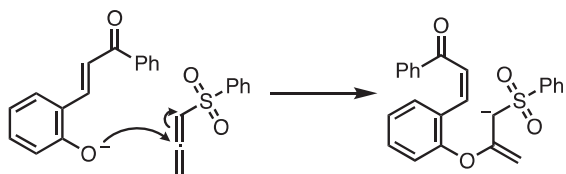
4– Base-catalysed loss of MeSH and water leads to the final aromatic thiophene ring.

Kumar, S.V.; Muthusubramanian, S.; Menéndez, J.C.; and Perumal, S., *Beilstein J.Org.Chem.* **11**, 1707 (2015)

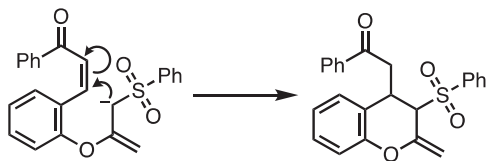
**Exercise 175**

1– The base produces elimination of HBr from the bromoallyl sulfone, delivering a highly reactive allenyl sulfone  $\text{H}_2\text{C}=\text{C}=\text{CHSO}_2\text{Ph}$ .

2– The deprotonated phenol adds to the allenyl sulfone.



3– The carbanion resulting from the previous addition reacts with the unsaturated ketone.



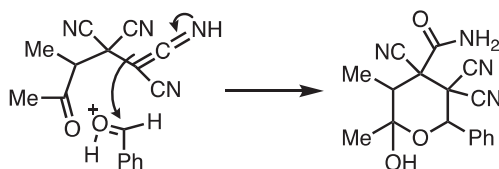
4– Base-catalysed migration of the alkene into conjugation with the sulfone gives rise to the final compound.

Thadkapally, S.; Kunjachan, A.C.; and Menon, R.S., *Beilstein J.Org.Chem.* **12**, 12 (2016)

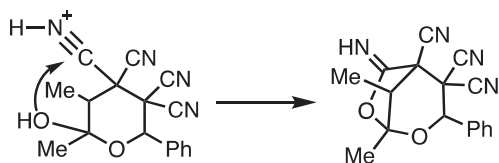
## Exercise 176

An apparently trivial condensation yielding a dihydropyran needs extra mechanistic scrutiny to explain the selective transformation of one cyanide to amide.

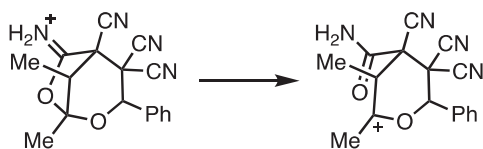
1– Condensation of the ketotetranitrile with benzaldehyde gives an alcohol that attacks the ketone resulting in a cyclic hemiacetal.



2– The hydroxy group of the hemiacetal attacks intramolecularly one of the cyanides.



3– The resulting iminoester is protonated leading to formation of the amide and a stable carbocation.

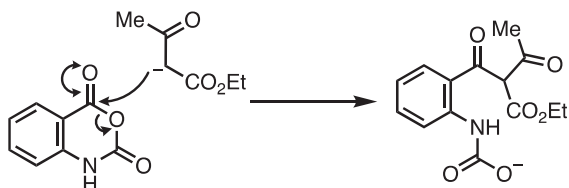


4– Deprotonation of the cationic species yields the final compound.

Ievlev, M.Y.; Ershov, O.V.; Belikov, M.Y. Milovidova, A.G.; Tafeenko, V.A.; and Nasakin, O.E. *Beilstein J.Org.Chem.* **12**, 2093 (2016)

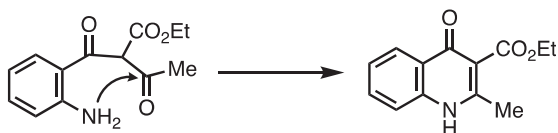
### Exercise 177

1– The enolate of ethyl acetoacetate attacks one of the carbonyls expelling the anion of a carbamic acid.



2– The carbamic acid releases carbon dioxide yielding an amine.

3– The amine condenses with the methyl ketone giving rise to a cyclic vinylogous amide with a very stable olefin that is conjugated with two carbonyl groups.



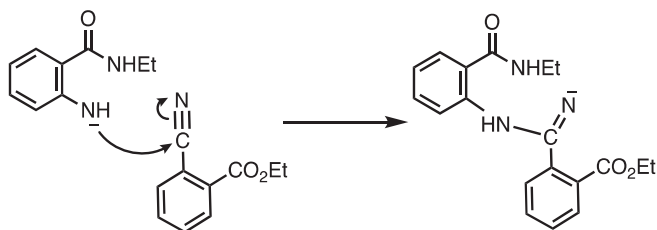
4– A final tautomerization delivers an aromatic pyridine ring

Jentsch, N.G.; Hume, J.D.; Crull, E.B.; Beauti, S.M.; Pham, A.H.; Pigza, J.A.; Kessl, J.J.; and Donahue, M.G., *Beilstein J.Org.Chem.* **14**, 2529 (2018)

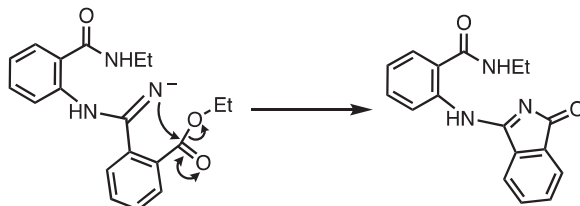
### Exercise 178

1– The very strong base  $\text{KHMDs}$  abstracts a proton from the amine generating a very nucleophilic amide anion.

2– This amide anion attacks the cyanide leading to an imine anion.



3– The imine anion attacks the ester and expels ethoxide.



4– Finally, after the amide is deprotonated, its nitrogen adds to the carbon-nitrogen double bond.

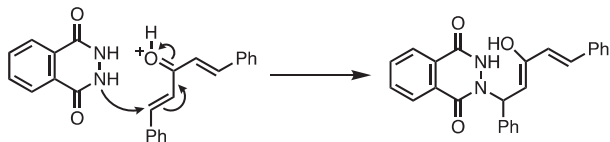
Venkateswarluab, R.; Murthya, V.N.; Tadiparthi, K.; Nikumbha, S.P.; Jinkalaa, R.; Siddaiahb, V.; Madhu babua, M.V.; Mohana, H.R.; and Raghunadh, A., *RSC Adv.* **10**, 9486 (2020)



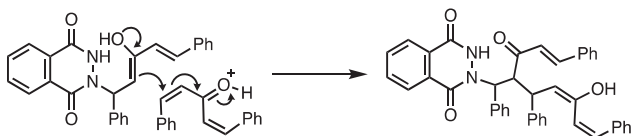
## Exercise 179

A cascade of Michael additions creates a convoluted molecule from unadorned starting compounds.

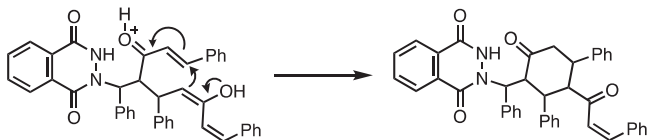
1– After protonation of the ketone, one of the nitrogen atoms attacks one of the olefins in the dienone.



2– The electron-rich alkene of the resulting enol attacks another protonated dienone.



3– The resulting enol attacks intramolecularly the protonated enone.

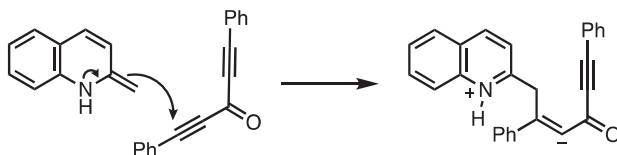


4– Condensation of one of the nitrogen atoms with one of the ketones delivers the final product.

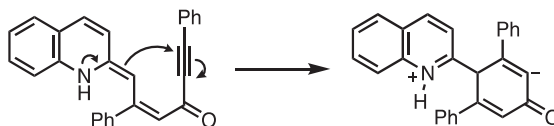
Xu, Y.-L.; Fu, J.-Y.; Liu, C.-H.; and Ding, T., *RSC Adv.*, **7**, 38733 (2017)

**Exercise 180**

- 1– The imine portion of the quinoline isomerizes to enamine.
- 2– The enamine performs a Michael addition on one of the ynones.



- 3– After transprotonation and isomerization to enamine, a second conjugate addition occurs.



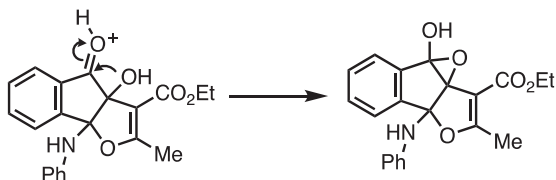
- 4– Transprotonation and isomerization to aromaticity supplies the final compound.

Zhao, H.-Y.; Wu, F.-S.; Yang, L.; Liang, Y.; Cao, X.-L.; Wang, H.-S.; and Pan, Y.-M., *RSC Adv.* **8**, 4584 (2018)

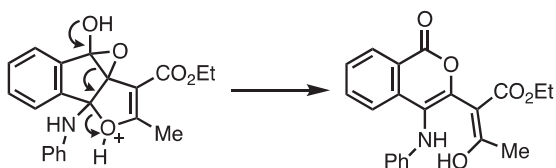
## Exercise 181

1– Protonation of the hydroxy group in the hemiacetal is followed by formation of a carbocation and delivery of water. The carbocation is trapped by aniline forming an intermediate hemiaminal ether.

2– Activation of the ketone by protonation promotes the intramolecular attack of the neighbouring alcohol yielding a hemiacetal in a three-membered ring.

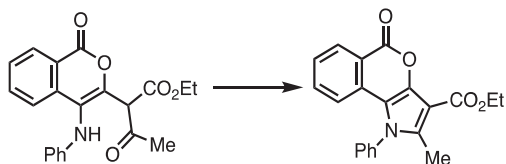


3– Protonation of the oxygen in the dihydrofuran activates an electronic flow that begins on the hydroxy group from the hemiacetal, produces the breakage of a carbon-carbon bond and liberates an enol.



4– The enol tautomerizes to ketone.

5– The ketone condenses with the amine forming an enamine inside an aromatic pyrrole ring.

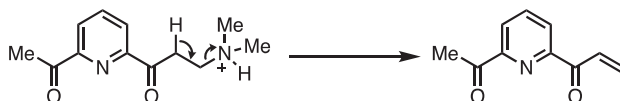


Pathak, S.; Debnath, K.; and Pramanik, A., *Beilstein J.Org.Chem.* **9**, 2344 (2013)

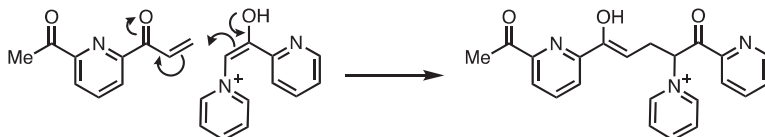
## Exercise 182

This is a variant of the so-called Kröhne pyridine synthesis, a synthesis in which pyridines are obtained by condensation between  $\alpha$ -pyridinium ketone salts and  $\alpha,\beta$ -unsaturated carbonyl compounds in the presence of a source of ammonia.

1– A reverse Michael addition in the ammonium chloride yields an  $\alpha,\beta$ -unsaturated ketone.

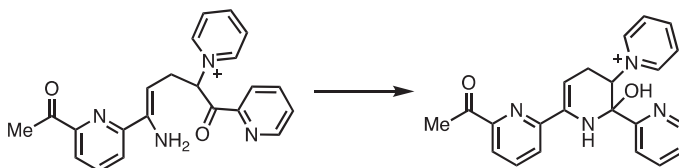


2– The enol tautomer of the  $\alpha$ -pyridinium ketone adds in a conjugated fashion to the  $\alpha,\beta$ -unsaturated ketone.



3– The resulting enol tautomerizes to a ketone that condenses with ammonia resulting in an enamine.

4– The enamine condenses with one of the ketones producing a tetrahydropyridine.



5– Loss of a pendant pyridinium residue and water produces the aromatization of the tetrahydropyridine to the final molecule possessing three pyridine rings.

Sasaki, I.; Daran, J.-C.; and Commenges, G., *Beilstein J.Org.Chem.* **11**, 1781 (2015)

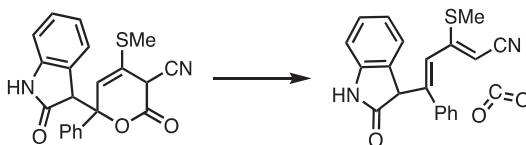
### Exercise 183

1– An anion is formed on  $\alpha$  to the carbonyl in indolone.

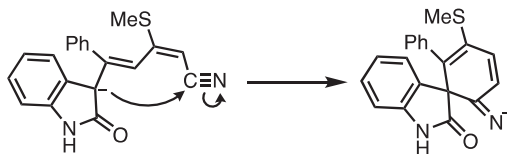
2– This carbanion adds to C-6 in the pyranone.



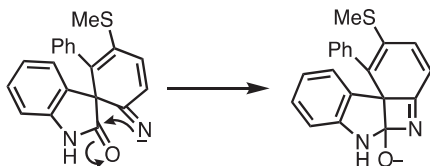
3– Protonation of the resulting anionic species provides an intermediate that loses  $\text{CO}_2$  through a retro-Diels-Alder reaction.



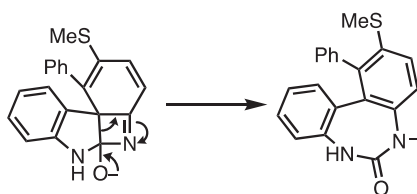
4– A carbanion, formed again on  $\alpha$  to the carbonyl of the indolone, adds to the cyanide.



5– The resulting negatively charged nitrogen reacts with the carbonyl of the indolone forming a four-membered ring.



6– The resulting unstable intermediate, possessing a negative charge on the oxygen and a tense four-membered ring, progresses by an electronic movement resulting in breaking of the four-membered ring and formation of a stable benzenic ring.

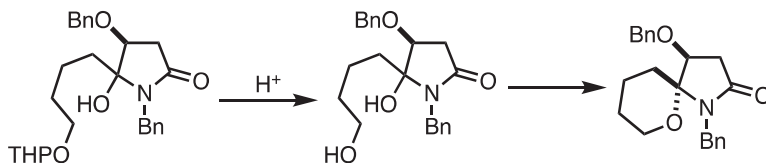


Kumar, S.; Pratap, R.; Kumar, A.; Kumar, B.; Tandon, V.K.; and Ram, V.J., *Beilstein J.Org.Chem.* **9**, 809 (2013)

## Exercise 184

1– The Grignard reagent adds to one of the carbonyl groups giving a hemiaminal.

2– *p*-Toluensulfonic acid deprotects the THP ether and causes a cyclization to the final aminal.

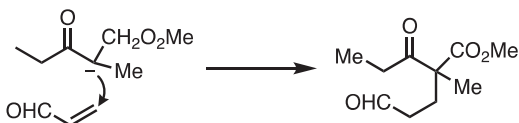


Zheng, J-F.; Chen, W.; Huang, S.-Y.; Ye, J.-L.; and Huang, P.-Q., *Beilstein J.Org.Chem.* **3**, No 41 (2007)

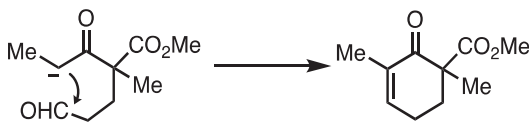
### Exercise 185

There is a Michael addition followed by an aldol reaction.

1– The enolate of the dicarbonylic compound adds in a conjugative way to acrolein.



2– After acidification and heating, there is an aldol condensation between the ketone and the aldehyde. Hydroquinone is probably added as a sacrificial reducing agent to avoid oxidation by adventitious air, or as a radical trap to avoid radical-induced decomposition.

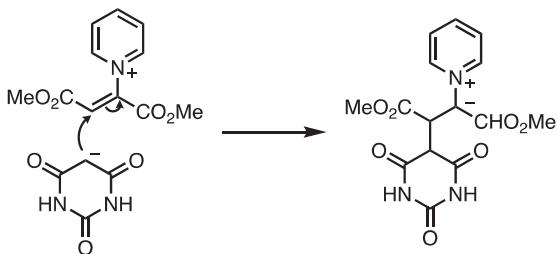


Dubberke, S.; Abbas, M.; and Westermann, B., *Beilstein J.Org.Chem.* **7**, 421 (2011)

### Exercise 186

1– Pyridine adds to dimethyl acetylenedicarboxylate.

2– The anion of barbituric acid adds to the resulting conjugated olefin.

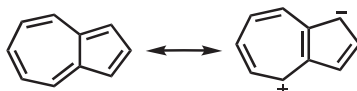


3– The resulting ylide evolves to a more stable zwitterionic compound.

Anary-Abbasinejad, M.; and Nejad-Shahrokhadi, F., *Arkivoc*, **6**, 149 (2019)

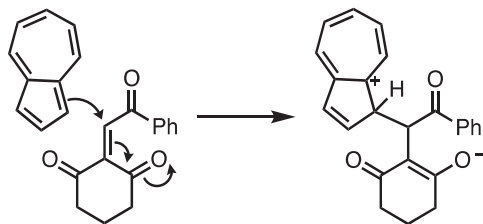
## Exercise 187

This reaction involves two rare occurrences: 1) azulene, a highly polarized hydrocarbon, and 2) an aldehyde that is stable as its hydrated geminal diol form because the non hydrated form contains two vicinal carbonyls unstabilizing each other by repulsion of charge. Azulene exists with a polarized resonant structure in which both rings contain six  $\pi$  electrons, and are therefore aromatic. This makes its five-membered ring very nucleophilic.



1– The aldehyde in equilibrium with the geminal diol condenses with the diketone yielding an olefin conjugated with three carbonyl groups.

2– There is a Michael reaction in which the nucleophile is the electron-rich five-membered ring in azulene and the electrophile is the electron-poor alkene conjugated with three carbonyl groups.



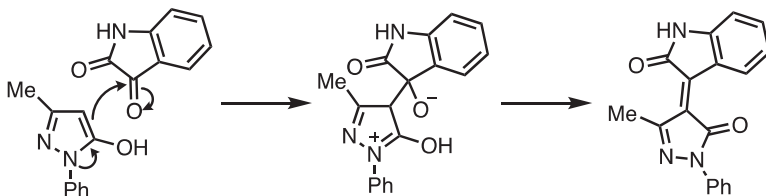
3– Transprotonation yields the final compound.

Gonga, J.; Peshkovb, A.A.; Yua, J.; Amandykovab, S.; Gimnkhanb, A.; Huang, J.; Kashtanovc, S.; Pereshivko, O.P.; and Peshkov, V.A., *RSC Adv.* **10**, 10113 (2020)



## Exercise 188

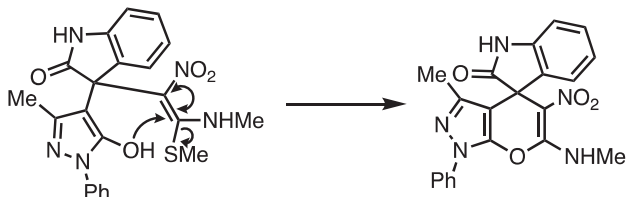
1– The enol tautomer of the pyrazolone attacks the ketone in isatin giving an alcohol that suffers dehydration. From another point of view, there is a condensation between an active methylene compound—the pyrazolone—and a very reactive ketone.



2– The resulting olefin is very electron-poor and prone to participate in Michael additions. Conversely, the olefin in the ketene thioaminal is electron-rich and attacks the previous olefin a la Michael.



3– After tautomerization, a highly polarized olefin is formed that contains a nitro and a methylthio group. Following basic reactivity principles, this olefin should be easily attacked by nucleophiles forming a carbanion stabilized by the nitro group that reverts to formation of the olefin and expulsion of thiomethoxide. The nucleophile operating here is the enol tautomer of the pyrazolone.

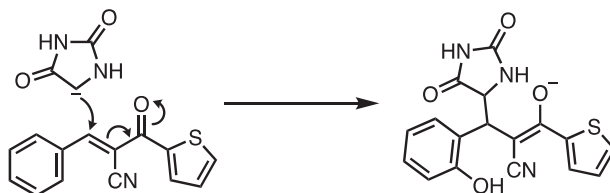


Mohammadi, A.; Bayat, M.; and Nasri, S., *RSC Adv.* **9**, 16525 (2019)

## Exercise 189

1– There is a condensation between the aldehyde and the  $\beta$ -cyano ketone. This leads to the formation of a very electron-poor olefin that reacts easily with nucleophiles.

2– The imidazolidinedione, which is a methylene-active compound, after deprotonation performs a Michael addition on the alkene.



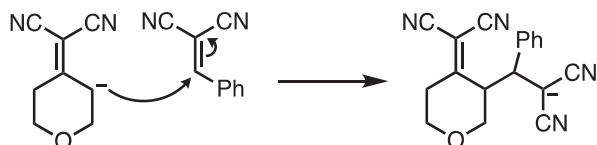
3– Subsequently, after transprotonation, a phenoxide is generated that attacks the cyanide, giving an imine that leads to the final compound by tautomerization.

Pazhanivel, L.; and Gnanasambandam, V., *RSC Adv.* **8**, 41675 (2018)

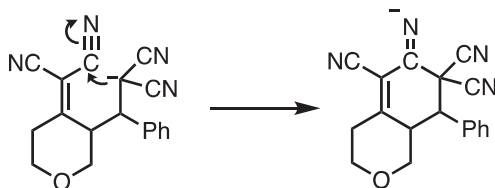
## Exercise 190

1– Malononitrile condensates independently with the ketone and with benzaldehyde.

2– A carbanion is formed on the tetrahydropyran ring at the  $\gamma$  position of both cyano groups. This carbanion effects a Michael addition to the product of the condensation of malononitrile with benzaldehyde.



3– The resulting carbanion reacts intramolecularly with one cyano group.



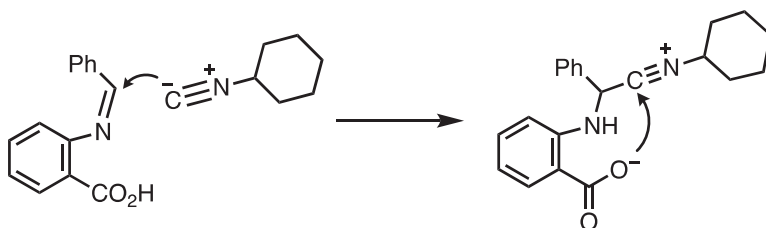
4– Transprotonations and base-induced elimination of HCN lead to the final aromatic compound.

Abae, M.S.; Forghani, S.; Mojtahedi, M.M.; and Hadizadeh, A., *Arkivoc*, **6**, 152 (2016)

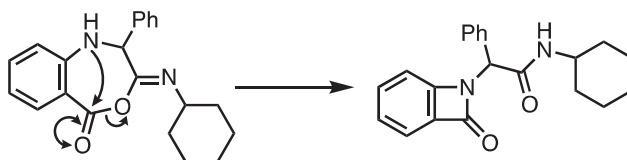
## Exercise 191

1- Condensation of the amine of anthranilic acid with benzaldehyde gives an imine.

2- Cyclohexyl isocyanate attacks this imine giving a highly electrophilic species with positively charged nitrogen that is attacked by the carboxylate.



3- The amine in the resulting seven-membered ring attacks the carbonyl expelling an amide. This results in the formation of a  $\beta$ -lactam.



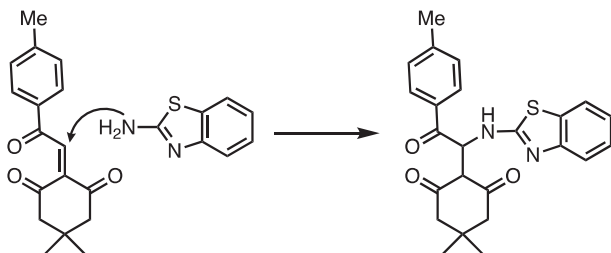
4- Methanol attacks the  $\beta$ -lactam yielding the final methyl ester.

It is possible to pose less convoluted mechanisms assuming the presence of adventitious water, but they hardly explain the formation of the methyl ester.

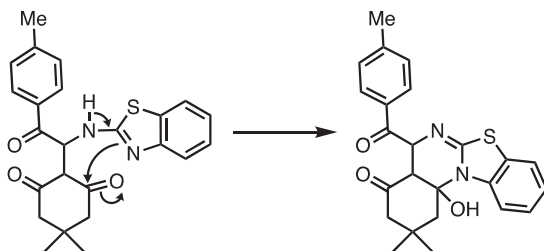
Poor, M.A.; Darehkordi, A.; Anary-Abbasinejad, M.; and Mohammadi, M., *Arkivoc*, **6**, 74 (2019)

**Exercise 192**

- 1– Dimedone condensates with the aldehyde.
- 2– The primary amine in 2-aminobenzothiazole effects a Michael addition to the product of the step above.



- 3– The second nitrogen makes a nucleophilic addition to a ketone producing a hemiaminal.



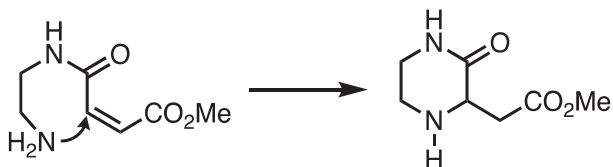
- 4– Dehydration and tautomerization provides the final product.

Alizadeh-Bami, F.; Mehrabi, H.; and Ranjbar-Karimi, R., *Arkivoc*, **6**, 228 (2019)

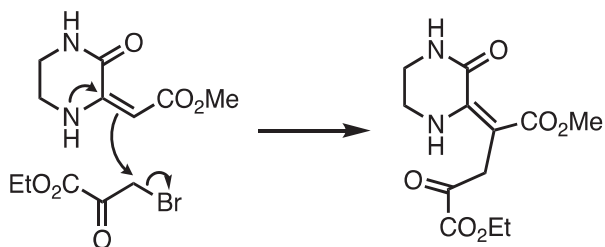
**Exercise 193**

1– One of the amines displaces one of the methoxy groups in dimethyl acetylenedicarboxylate yielding an amide.

2– The other amine adds intramolecularly in a conjugated fashion to the alkene in the unsaturated ester.



3– The enamine moiety in the resulting molecule is C-alkylated by the bromide.



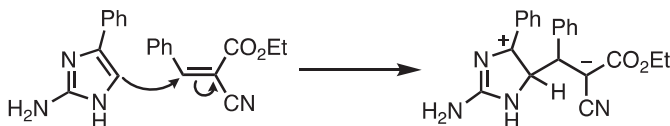
4– Condensation of the amine with the ketone and removal of water provides the pyrrole ring in the final product.

Piltan, M.; Moradi, L.; Abasi, G.; and Zarei, S.A., *Beilstein J.Org.Chem.* **9**, 510 (2013)

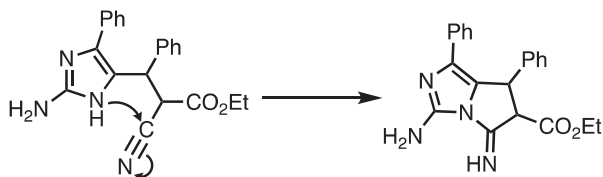
## Exercise 194

1– Ethyl cyanoacetate condenses with benzaldehyde producing a very good Michael acceptor with a polarized olefin conjugated with an ester and a cyanide.

2– The imidazol ring, which is highly nucleophilic due to the activating effect of the amine, attacks the Michael acceptor.



3– After transfer of protons including rearomatization of the imidazole, a nitrogen in the imidazole attacks intramolecularly the cyanide.



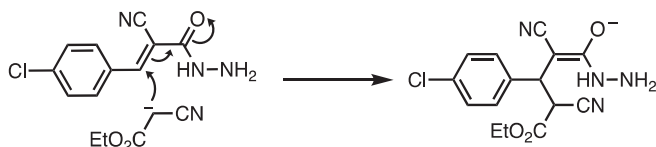
4– Finally, a carbon-nitrogen double bond migrates into conjugation with the carbonyl of an ester.

Lipson, V.V.; Pavlovska, T.L.; Svetlichnaya, N.V.; Poryvai, A.A.; Gorobets, N.Y.; Van der Eycken, E.V.; Konovalova, I.S.; Shiskina, S.V.; Borisov, A.V.; Musatov, V.I.; and Mazepa, A.V., *Beilstein J.Org.Chem.* **15**, 1032 (2019)

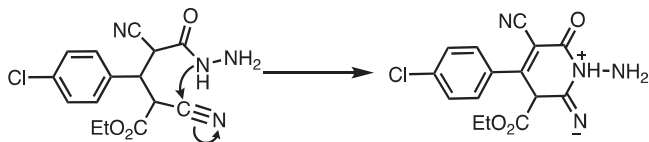
### Exercise 195

1– Under the action of the base piperidine, 2-cyanoacetohydrazide condenses with the aldehyde giving rise to a very electrophilic alkene.

2– The anion of ethylcyanoacetate attacks the electrophilic alkene a la Michael.



3– After protonation, one of the nitrogens of the acylhydrazine attacks one of the cyanides.



4– Transprotonation and migration of the double bond delivers the final compound.

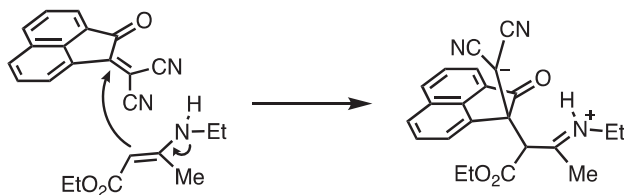
Hosseini, H; and Bayat, M., *RSC Adv.* **8**, 27131 (2018)



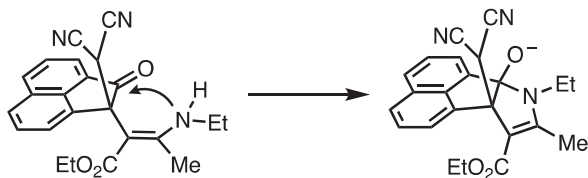
## Exercise 196

1– An enamine is formed by condensation of ethanamine with ethyl acetylacetae.

2– The enamine adds a la Michael to the exceedingly electron-poor alkene containing two cyanide groups.



3– After tautomerization, the nitrogen atom attacks the ketone.



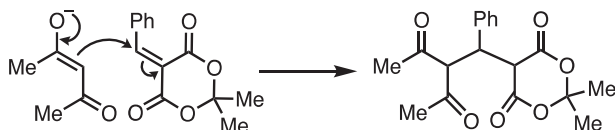
4– The resulting alkoxide attacks one of the nitriles, supplying the final product after tautomerization.

Beyrati, M.; and Hasaninejad, A., *RSC Adv.* **8**, 14171 (2018)

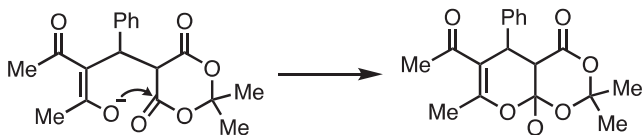
## Exercise 197

1– Meldrum's acid is condensed with benzaldehyde giving an alkene that is highly activated by conjugation with two esters.

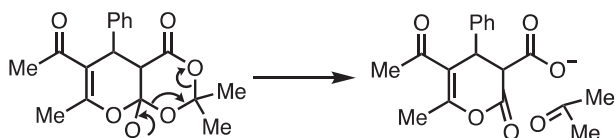
2– The enolate of acetylacetone adds to this olefin.



3– An enolate is formed on the  $\beta$ -diketone moiety of the molecule and it adds via oxygen to the carbonyl of one of the esters.



4– The resulting tetrahedral intermediate containing an alkoxide anion suffers a fragmentation promoted by the generation of a stable carboxylate anion. This fragmentation leads to the liberation of acetone.



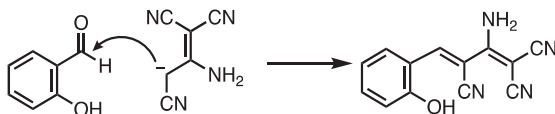
5– The carboxylate suffers a facile decarboxylation promoted by the evolution of carbon dioxide and the formation of a carbanion stabilized by a carbonyl group. Protonation of the resulting carbanion yields the final product.

Note: the fragmentation with evolution of acetone and the decarboxylation might happen concurrently.

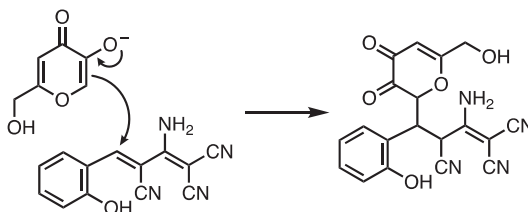
Mehrabi, H.; Najafian-Ashrafi, F.; and Ranjbar-Karimi, R.,  
*Arkivoc*, **3**, 191 (2018)

### Exercise 198

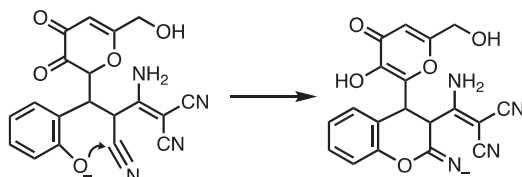
1– Under the basic conditions provided by potassium fluoride, a carbanion is formed on  $\alpha$  to one cyanide group in the reactant on the right and it condenses with the aldehyde.



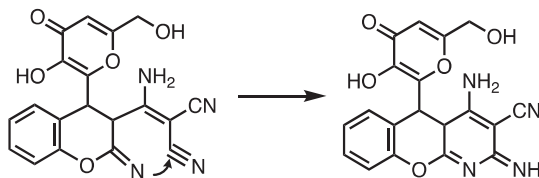
2– The anion of kojic acid effects a Michael addition to an unsaturated cyanide.



3– Enolization of a ketone and attack of phenoxide to neighbouring cyanide provides a new intermediate.



4– The resulting imidate attacks intramolecularly a cyanide.



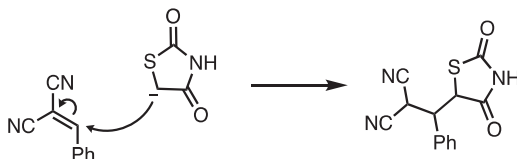
5– Tautomerization and protonation provides the final product.

Elinson, M.N.; Vereshchagin, A.N.; Anisina, Y.E.; Krymov, S.K.; Fakhрутdinov, A.N.; and Egorov, M.P., *Arkivoc*, **2**, 38 (2019)

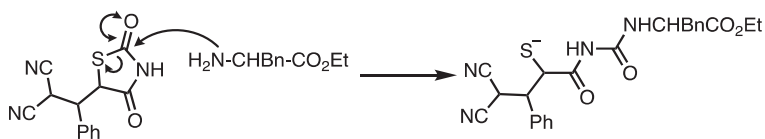
## Exercise 199

1– Benzaldehyde condenses with malononitrile giving a good Michael acceptor.

2– Triethylamine forms a carbanion on the thiazolidinedione. This carbanion performs a conjugated addition on the Michael acceptor formed above.



3– The deprotonated amine in the amino acid ethyl ester attacks one of the carbonyls in the thiazolidinedione expelling the sulfur atom as a sulfide.

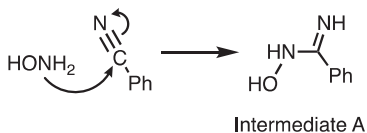


4– The sulfide attacks one of the nitrile groups delivering a cyclic imidothioate that tautomerizes to the final compound.

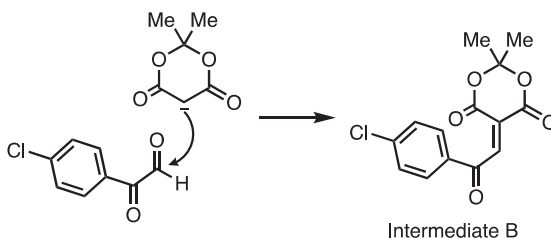
Sun, J.; Zhang, Y.; and Yan, C.-G., *RSC Adv.* **8**, 22498 (2018)

## Exercise 200

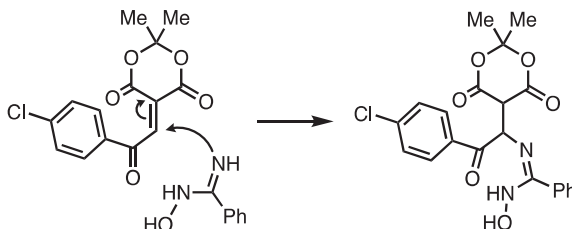
1– Hydroxylamine adds to benzyl cyanide.



2– Meldrum's acid condensates with the aldehyde.



3– There is a Michael addition between intermediates A and B.



4– Finally, a condensation of a hydroxylamine derivative and a ketone followed by tautomerization yields the product.

Alizadeh-Bami, F.; Salehzadeh, M.; Mehrabi, H.; and Ranjbar-Karimi, R.; *Arkivoc*, **6**, 55 (2019)

# GLOSSARY

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