Two Hundred Exercises in Mechanistic Organic Chemistry

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By

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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.

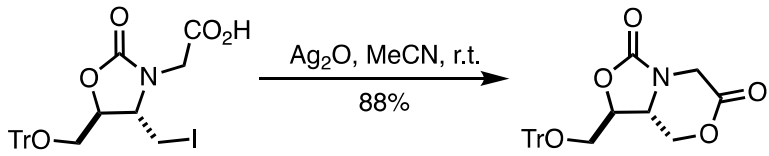
ABBREVIATIONS

Ac	acetyl, $CH_3C(=O)$–
aq.	aqueous
Bn	benzyl, $PhCH_2$–
Boc	*tert*-butoxycarbonyl, *t*-BuOC(=O)–
Bu	*n*-butyl
i-Bu	isobutyl, $(CH_3)_2CH\text{-}CH_2$–
t-Bu	*tert*-butyl, Me_3C–
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	*p*-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide, MeS(=O)Me
Et	ethyl, CH_3CH_2–
KHMDS	$KN(SiMe_3)_2$
LHMDS	$LiN(SiMe_3)_2$
MCPBA	*m*-choroperoxybenzoic acid
Me	methyl, CH_3–
Ms	mesyl, $MeSO_2$–
NBS	*N*-bromosuccinimide
Pd/C	palladium on activated carbon
Ph	phenyl
Piv	pivaloyl, $Me_3CC(=O)$–
PMB	*p*-methoxybenzyl, *p*-$MeOC_6H_4CH_2$–
PMP	*p*-methoxyphenyl, *p*-$MeOC_6H_4$–
Py	pyridine
i-Pr	isopropyl, Me_2CH–
ref.	reflux
r.t.	room temperature
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl, *t*-$BuPh_2Si$–
TBS	*tert*-butyldimethylsilyl, *t*-$BuMe_2Si$–

TES	triethylsilyl, Et_3Si–
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl, Me_3Si–
Tr	triphenylmethyl (trityl), Ph_3C–
Ts	*p*-toluenesulfonyl, *p*-$MeC_6H_4SO_2$–

EXERCISES

Exercise 1



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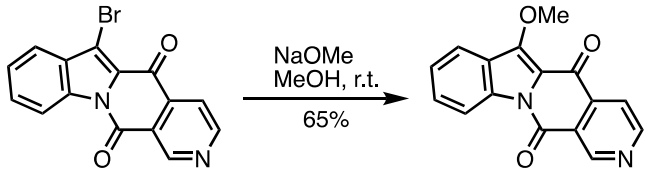

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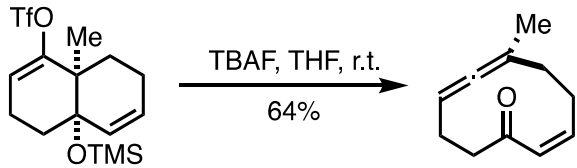

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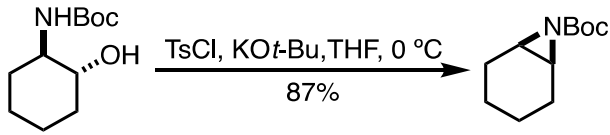

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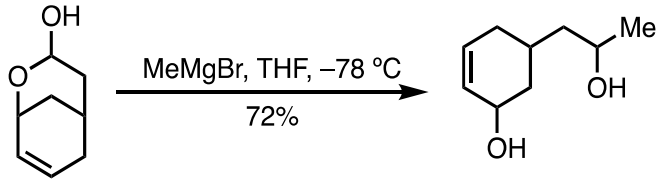

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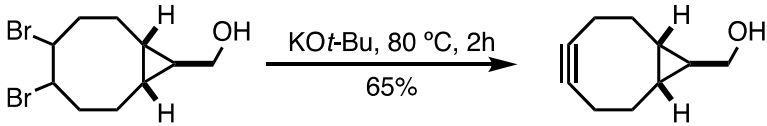

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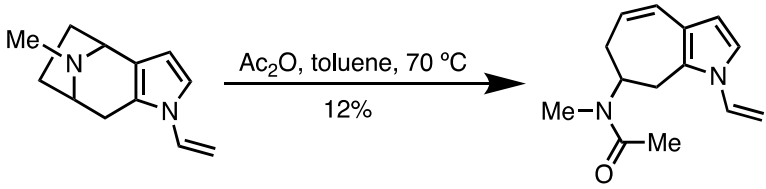

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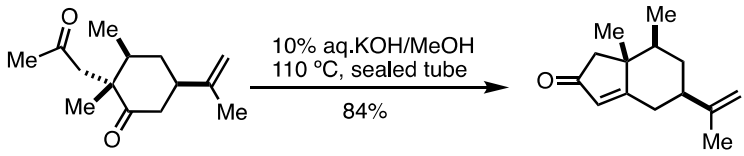

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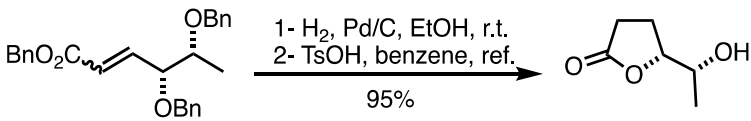

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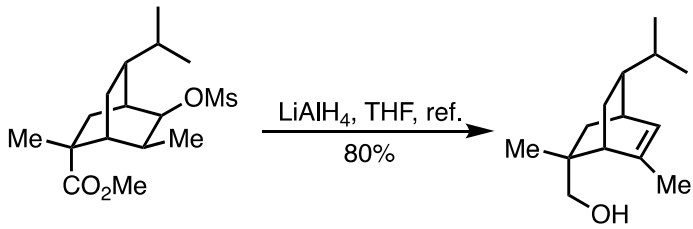

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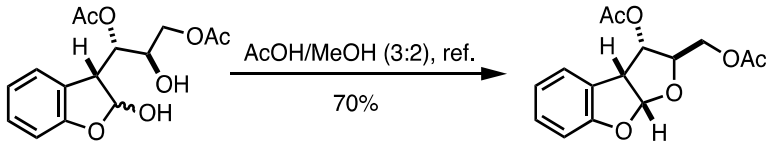

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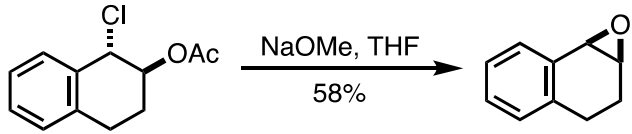

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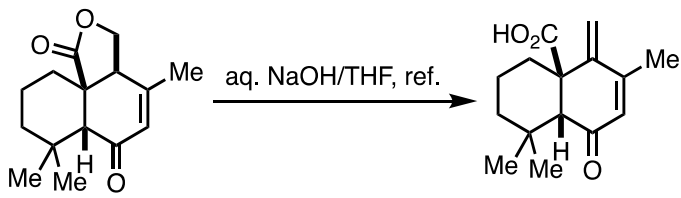

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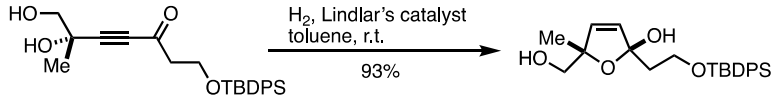

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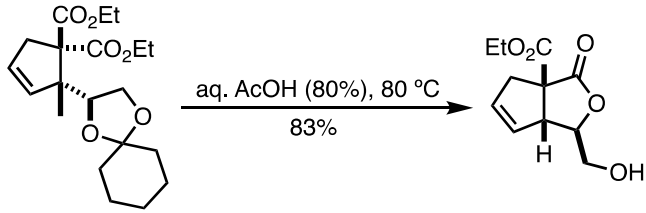

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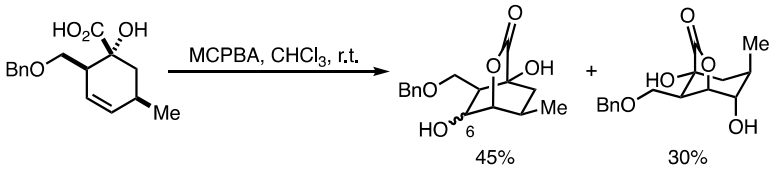

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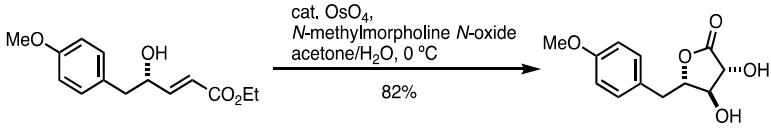

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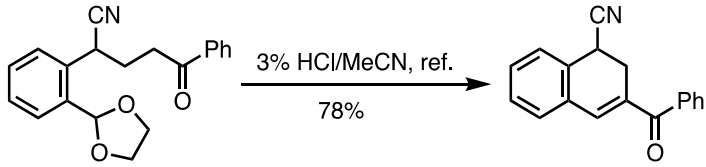

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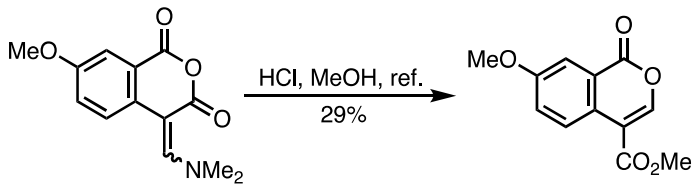

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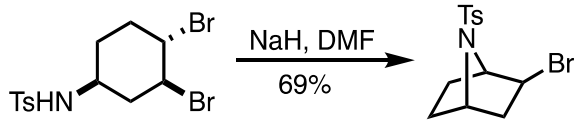

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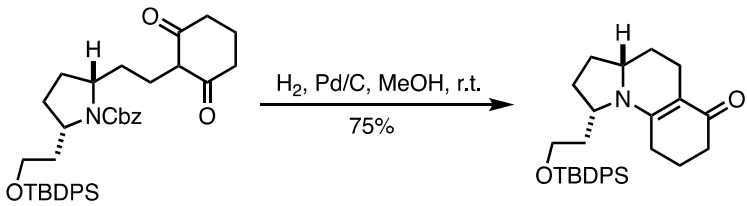

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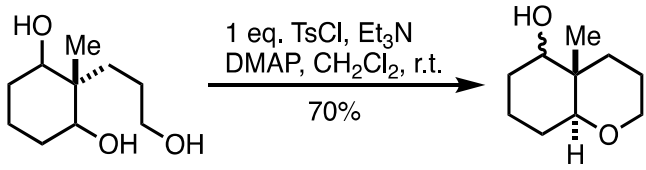

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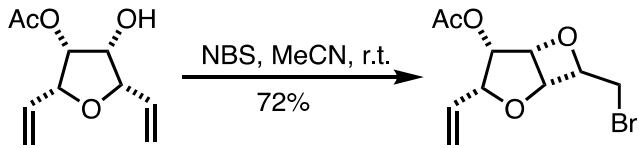

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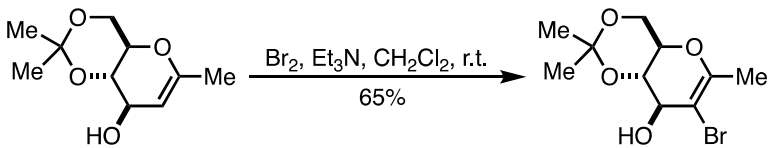

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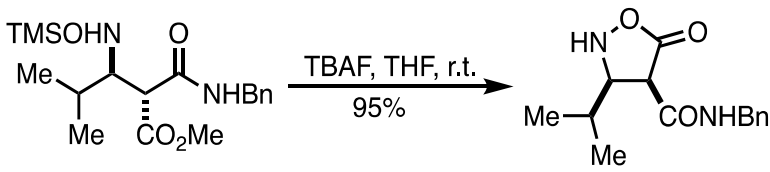

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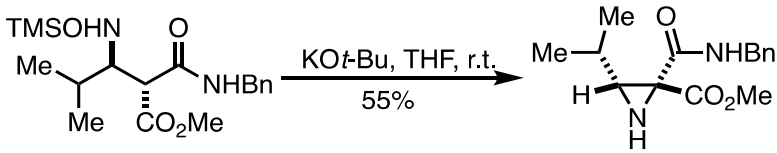

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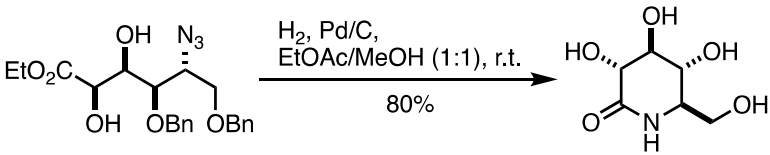

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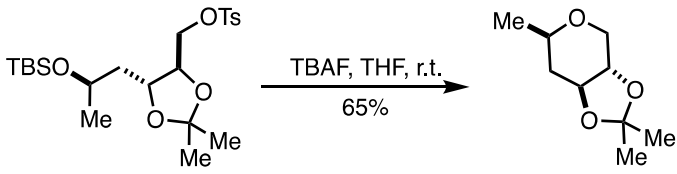

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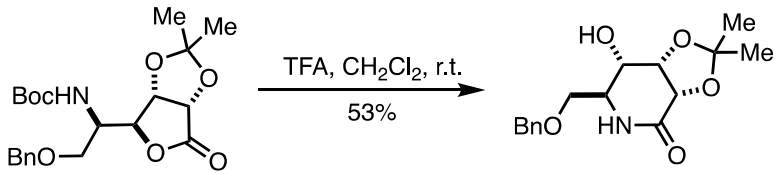

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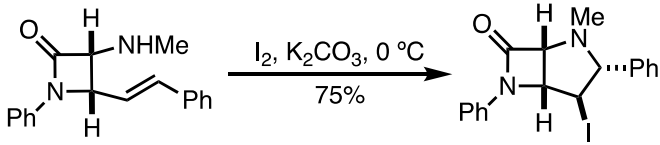

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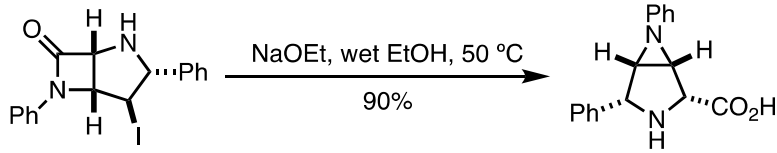

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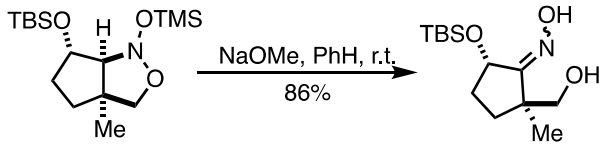

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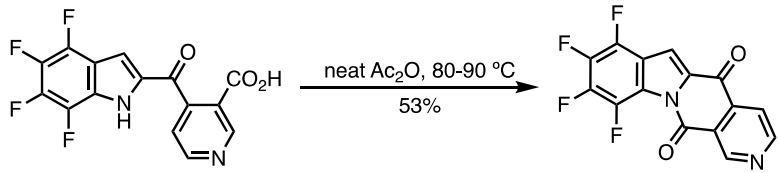

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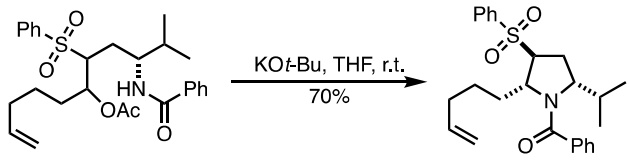

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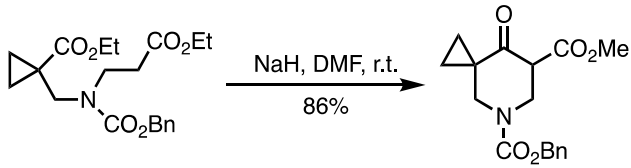

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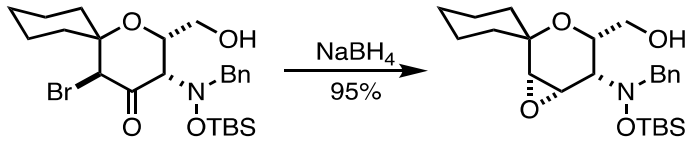

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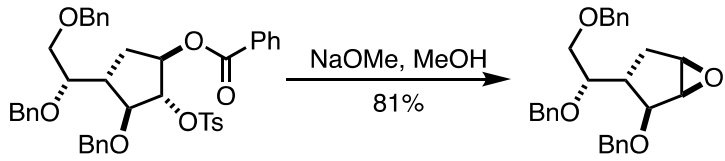

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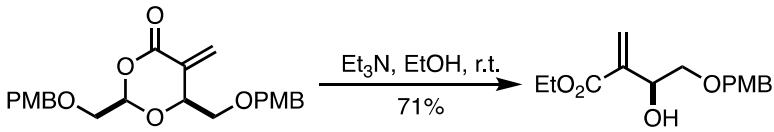

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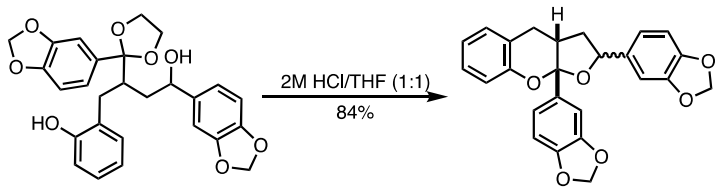

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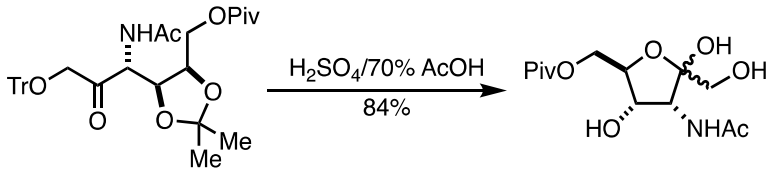

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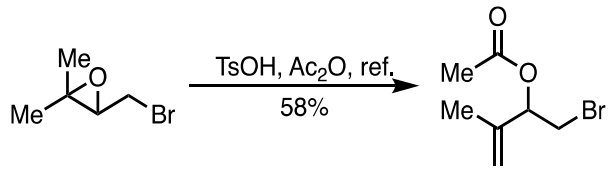

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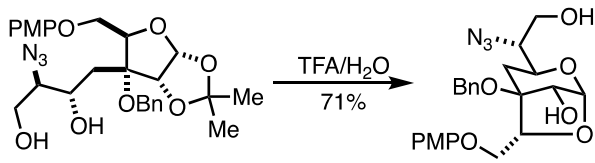

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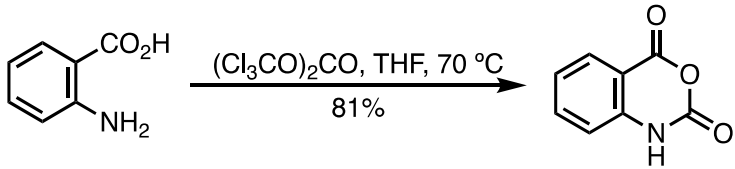

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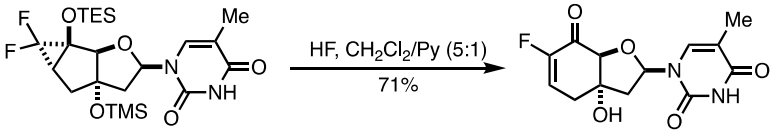

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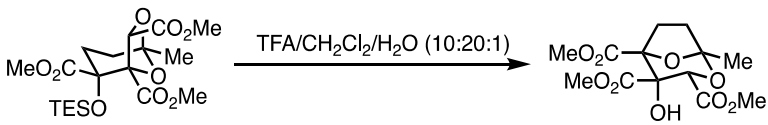

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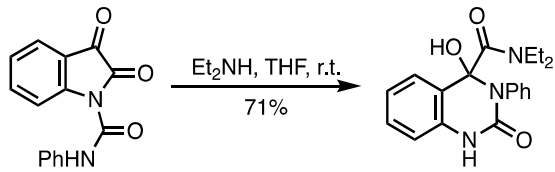

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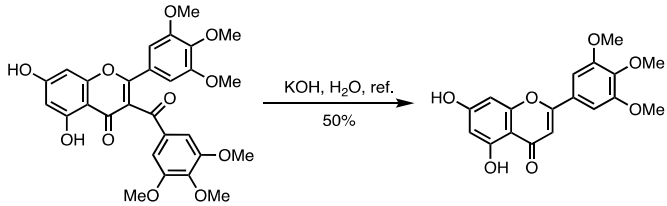

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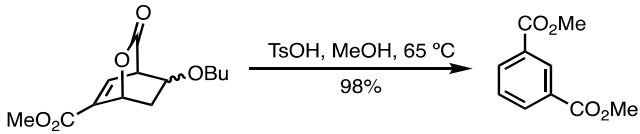
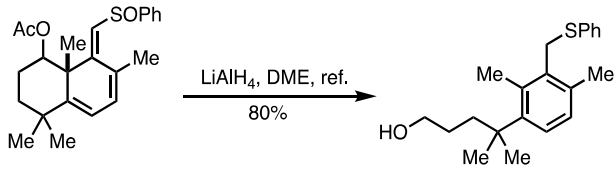
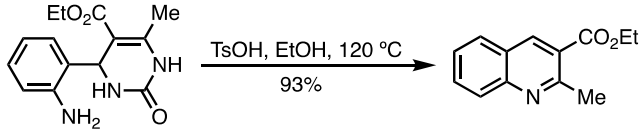


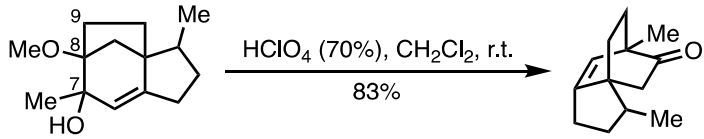
Exercise 50



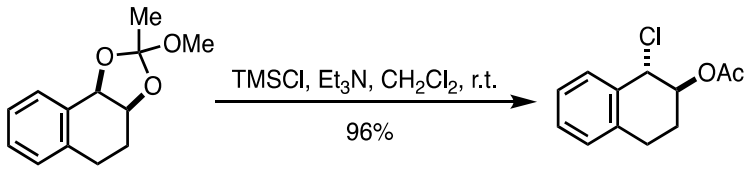
Exercise 51



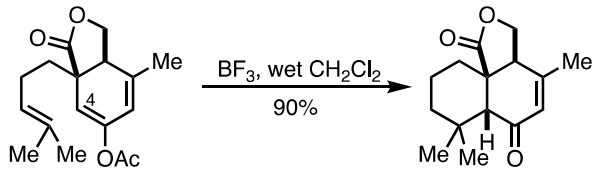
Exercise 52



Exercise 53



Exercise 54



Exercise 55