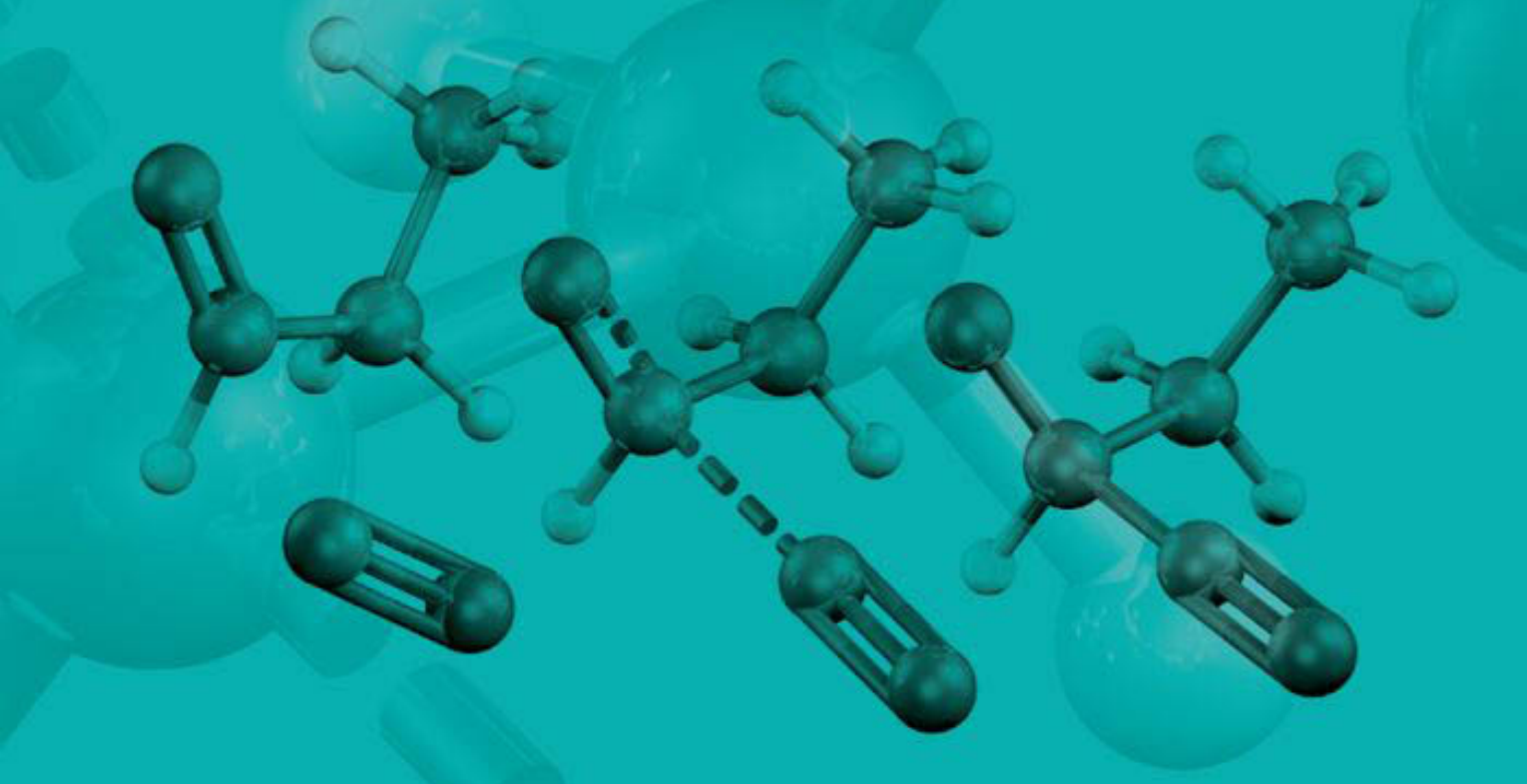
OXFORD

Solutions manual to accompany

ORGANIC CHEMISTRY

SECOND EDITION



Jonathan Clayden and Stuart Warren

Solutions manual to accompany

Organic Chemistry

Second Edition

Jonathan Clayden, Nick Greeves, and Stuart Warren

Jonathan Clayden
University of Manchester

Stuart Warren
University of Cambridge

OXFORD
UNIVERSITY PRESS

OXFORD
UNIVERSITY PRESS

Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide. Oxford is a registered trade mark of
Oxford University Press in the UK and in certain other countries

First edition published 2001

Impression: 1

British Library Cataloguing in Publication Data
Data available

978–0–19–966334–7

Printed in Great Britain by

Ashford Colour Press Ltd, Gosport, Hampshire

Suggested solutions for Chapter 2

2

PROBLEM 1

Draw good diagrams of saturated hydrocarbons with seven carbon atoms having (a) linear, (b) branched, and (c) cyclic structures. Draw molecules based on each framework having both ketone and carboxylic acid functional groups in the same molecule.

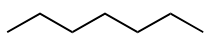
Purpose of the problem

To get you drawing simple structures realistically and to steer you away from rules and names towards more creative and helpful ways of representing molecules.

Suggested solution

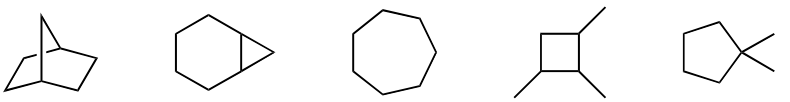
There is only one linear hydrocarbon but there are many branched and cyclic options. We offer some possibilities, but you may have thought of others.

linear saturated hydrocarbon (*n*-heptane)



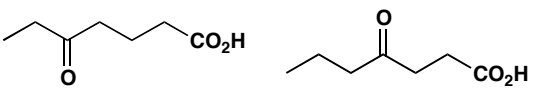
some branched hydrocarbons

some cyclic hydrocarbons

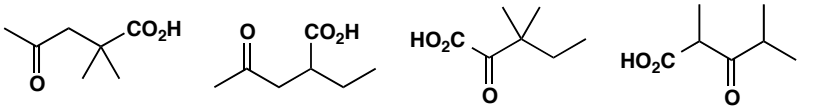


We give you a few examples of keto-carboxylic acids based on these structures. A ketone has to have a carbonyl group not at the end of a chain; a carboxylic acid functional group by contrast *has* to be at the end of a chain. You will notice that no carboxylic acid based on the first three cyclic structures is possible without adding another carbon atom.

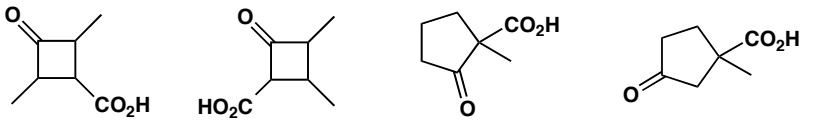
linear molecules containing ketone and carboxylic acid



some branched keto-acids

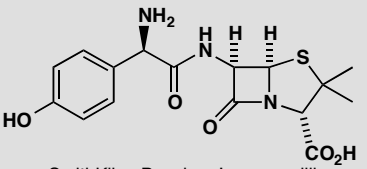


some cyclic keto-acids

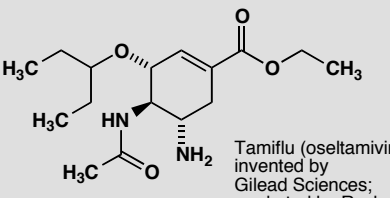


PROBLEM 2

Draw for yourself the structures of amoxicillin and Tamiflu shown on page 10 of the textbook. Identify on your diagrams the functional groups present in each molecule and the ring sizes. Study the carbon framework: is there a single carbon chain or more than one? Are they linear, branched, or cyclic?



SmithKline Beecham's amoxycillin
β-lactam antibiotic
for treatment of bacterial infections



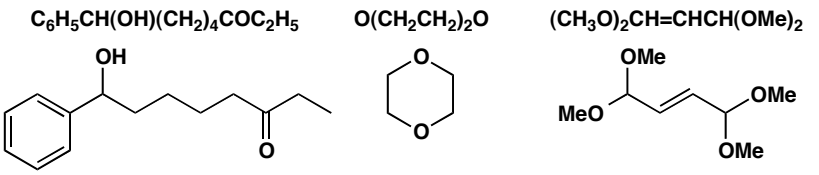
Tamiflu (oseltamivir):
invented by
Gilead Sciences;
marketed by Roche

Purpose of the problem

To persuade you that functional groups are easy to identify even in complicated structures: an ester is an ester no matter what company it keeps and it can be helpful to look at the nature of the carbon framework too.

Suggested solution

The functional groups shouldn't have given you any problem except perhaps for the sulfide (or thioether) and the phenol (or alcohol). You should have seen that both molecules have an amide as well as an amine.



PROBLEM 7

Identify the oxidation level of all the carbon atoms of the compounds in problem 6.

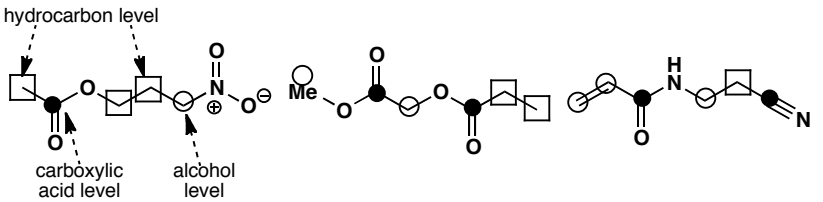
Purpose of the problem

This important exercise is one you will get used to very quickly and, before long, do without thinking. If you do it will save you from many trivial errors. Remember that the oxidation *state* of all the carbon atoms is +4 or C(IV). The oxidation *level* of a carbon atom tells you to which oxygen-based functional group it can be converted without oxidation or reduction.

Suggested solution

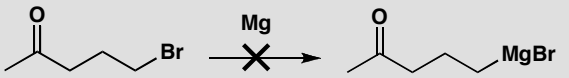
Just count the number of bonds between the carbon atom and heteroatoms (atoms which are not H or C). If none, the atom is at the hydrocarbon level (□), if one, the alcohol level (○), if two the aldehyde or ketone level, if three the carboxylic acid level (●) and, if four, the carbon dioxide level.

■ Why alkenes have the alcohol oxidation level is explained on page 33 of the textbook.



PROBLEM 5

In the textbook (p. 228) we say that the Grignard reagent below is 'an unstable structure—impossible to make.' Why is this? What would happen if you tried to make it?

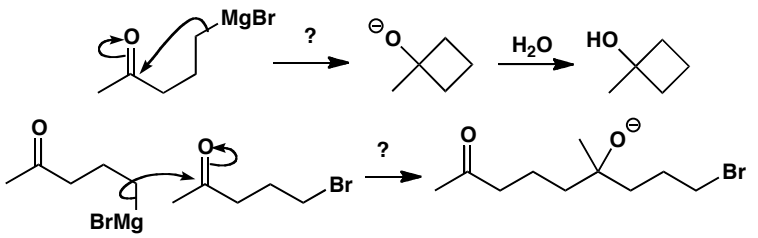


Purpose of the problem

Revision of the danger of mutually destructive functional groups.

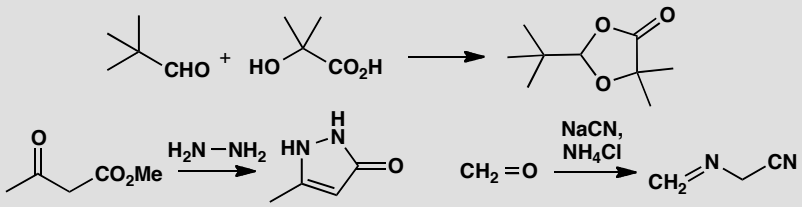
Suggested solution

There are various possibilities that all arise from the presence of a carbonyl group and a Grignard in the same molecule. These two would react together. They might cyclize to form a four-membered ring or a bimolecular reaction might lead to a dimer and perhaps polymerization.



PROBLEM 6

Suggest mechanisms for these reactions.

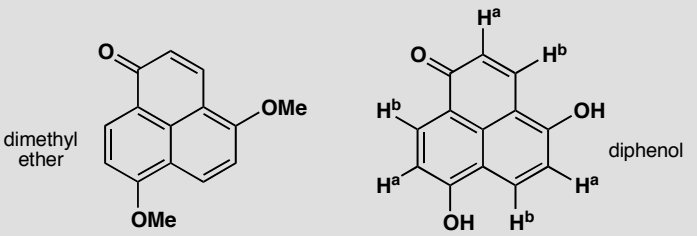


Purpose of the problem

Extension of acetal and imine formation into examples where the intermediate is trapped by a different nucleophile.

PROBLEM 3

The NMR spectrum of this dimethyl ether is complicated: the two MeO groups are different as are all the hydrogen atoms on the rings. However the diphenol has a very simple NMR spectrum—there are only two types of proton on the rings marked 'a' and 'b' on the diagram. Explain.



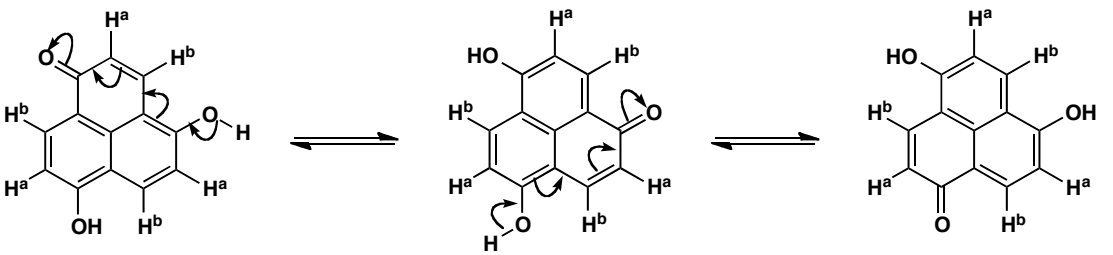
Purpose of the problem

Exploring the way that tautomerism leads to equivalence.

Suggested solution

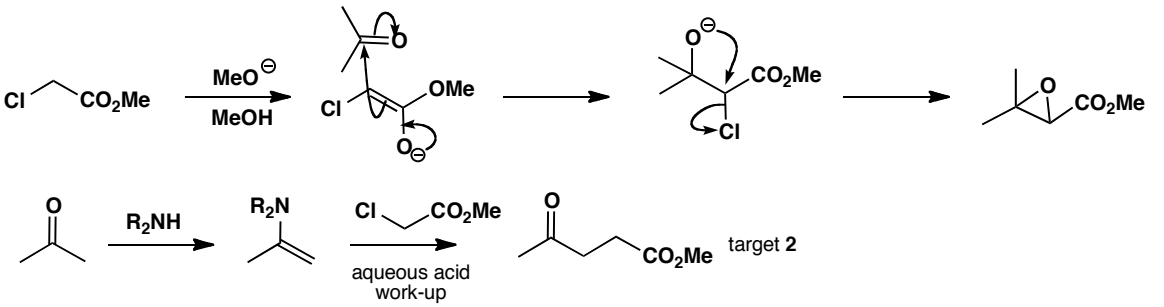
The protons in the ether are obviously all different as it has no symmetry. Tautomerization interconverts carbonyl groups and enols, and can make either of the enols in the diphenol into a carbonyl group and can make the carbonyl group into an enol, so all structures are equivalent. If this proton transfer (note that it is *not* a delocalization) is fast on the NMR time scale, all the H^as will appear in one signal and all the H^bs will appear in another signal.

■ The idea that some interconversions take place too fast to be detected by NMR (they are fast on the NMR timescale) is covered in the blue boxes on p. 363 and p. 374 of the textbook.



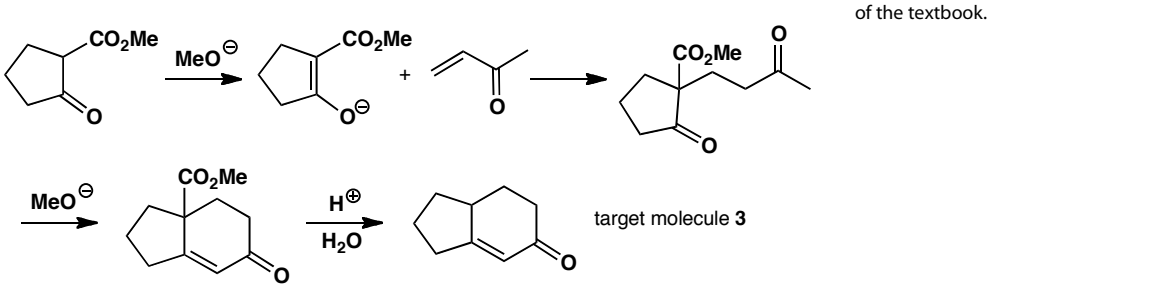
that occurred is the Darzens condensation. To avoid this problem use a specific enolate of the ketone such as an enamine or a β-ketoester.

■ The Darzens condensation is on p. 639 of the textbook.



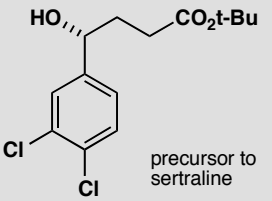
In the third case, the cyclopentanone has self-condensed and ignored the enone. The answer again is to use a specific enolate, such as the easily made β-keto-ester below. The six-membered ring is then easily formed by intramolecular aldol reaction. These two reactions together make a Robinson annelation. Finally the CO_2Me group must be removed by hydrolysis and decarboxylation.

■ The Robinson annelation: p. 638 of the textbook.

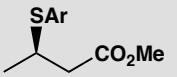


PROBLEM 9

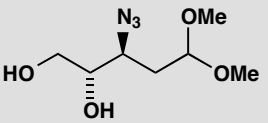
Propose catalytic methods for the asymmetric synthesis of these four precursors to drug molecules.



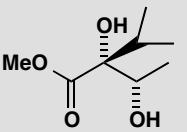
precursor to sertraline



precursor to MK-0507



precursor to AZT



precursor to indicine

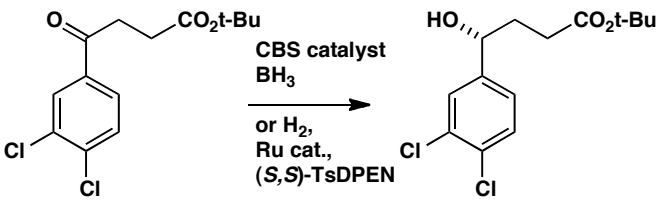
Purpose of the problem

Identifying reliable catalytic reactions that give desired structural features.

Suggested solution

The sertraline precursor is a chiral alcohol with the stereogenic centre adjacent to an aromatic ring. An obvious approach is to make the hydroxyl group by asymmetric reduction of the corresponding ketone. CBS reduction is a possibility, as is a ruthenium-catalysed hydrogenation using the ligand TsDPEN (p. 1115 of the textbook).

■ You should not try to remember which enantiomer of the ligand you need for which enantiomer of the product: that can easily be looked up later. It is much more important to recognize the classes of molecules that can be reliably prepared by catalytic asymmetric reactions.



The second compound is a chiral sulfide. Although there are direct asymmetric ways of making chiral sulfur compounds, a reliable approach to sulfides is to use S_N2 substitution of a more readily made chiral precursor, because a thiolate is usually a good nucleophile. The S_N2 reaction goes with inversion, so we need the chiral alcohol shown below, converted to a derivative (such as a tosylate) capable of undergoing substitution. Care will be needed to avoid elimination, but thiolates are excellent nucleophiles and not too basic, so you would expect a successful outcome.