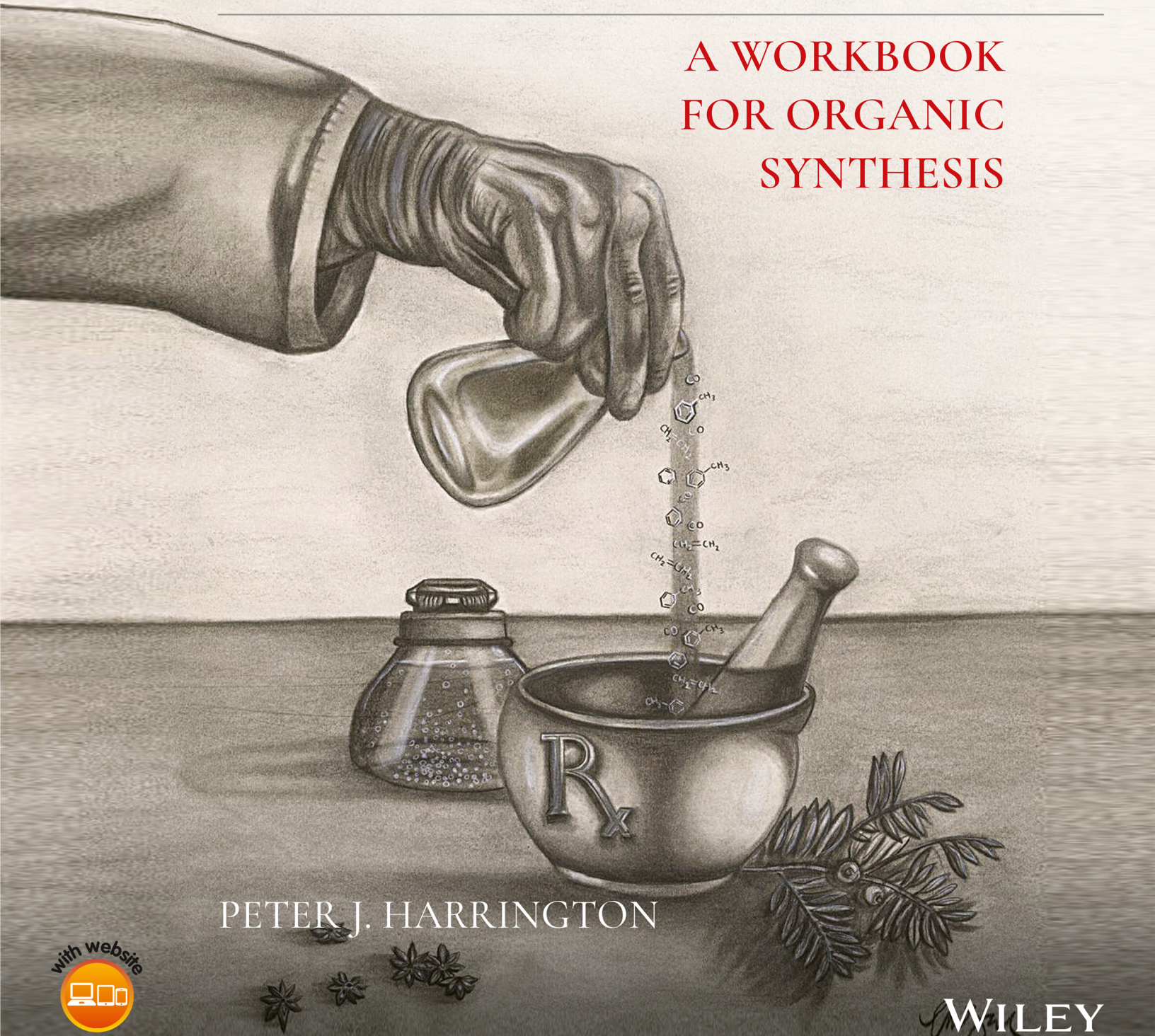
ROUTES TO ESSENTIAL MEDICINES

A WORKBOOK FOR ORGANIC SYNTHESIS



PETER J. HARRINGTON

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Routes to Essential Medicines

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A Workbook for Organic Synthesis

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WILEY

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This workbook is dedicated to everyone who made it their mission in life to discover and manufacture Essential Medicines and to:
Professor Louis S. Hegedus

Who inspired this workbook project with a lesson learned at Colorado State University:
An hour in the library will save you from two weeks of floundering around in the laboratory.

About the Companion Website

www.wiley.com/go/Harrington/routes_essential_medicine

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Introduction

While teaching undergraduate Organic Chemistry at University of Colorado, I was asked if I could teach a course in organic synthesis. I have worked as synthetic organic chemist and educator for my entire career (Princeton University, Colorado State University, SUNY Binghamton, Syntex, Roche, University of Denver, University of Colorado, and Better Pharma Processes, LLC) but I realized I was not prepared to teach the course. This workbook project began with that missed opportunity.

In my first Organic Chemistry class at Canisius College more than forty years ago, I recognized the power synthetic organic chemists have to create new medicines to improve human healthcare. With great power comes great responsibility. The synthetic organic chemistry community accepted this responsibility: the result is our World Health Organization (WHO) Model List of Essential Medicines.

Routes to Essential Medicines: A Workbook for Organic Synthesis highlights the synthetic organic chemistry in the manufacturing routes of nearly three hundred medicines on the World Health Organization (WHO) Model List of Essential Medicines (20th List from March 2017). The workbook includes all the medicines on the list for which synthetic organic chemistry plays an important role in the manufacturing process.

Routes to Essential Medicines: A Workbook for Organic Synthesis is intended for use by upper-level undergraduate students and graduate students participating in a course in organic synthesis or medicinal chemistry. Students using this workbook will become familiar with the structures and synthetic challenges associated with nearly three hundred essential medicines and gain an appreciation for the manufacture of specialty chemical starting materials. Students who use this workbook will develop a solid foundation for their academic and postacademic research: an extensive favorites list of key journal and information sites and a personal library of reagents, solvents, and conditions for many workhorse organic reactions. Classroom discussion and extended discussion time will provide valuable experience presenting route and reagent options and mechanisms.

For many students, this workbook will be a first encounter with the Essential Medicines on the WHO List. These medicines are the milestones in our progress in improving human healthcare in the last 100 years. The structural features of these medicines and the synthetic strategies used to create these medicines are the current state of the art and the foundation we will build upon to move human healthcare ahead for the next 100 years. How important are the Essential Medicines? In 2020 they are critically important. They are life-and-death important. I look out my office window on a world practicing social distancing to slow the spread of covid19. We wait for "the answer," a drug to speed recovery from the infection, better yet, a drug to stop the spread of the virus. An optimal drug would be a drug with known and tolerable side effects, a drug which can be produced and distributed quickly, an inexpensive drug. This description fits many of the Essential Medicines on the WHO List so it comes as no surprise that many of the medicines in this workbook are being evaluated as an answer for covid19.

Workbook Organization

The workbook is organized by INN (International Non-Proprietary Name) of the essential medicines in alphabetical order. The presentation for each target molecule begins with the structure of the target and the indications for the drug taken from the Model List. For example, for amiodarone:

From the List:

12. Cardiovascular Medicines
12.3 Antihypertensive Medicines

In the workbook:

Cardiovascular Medicines/Antihypertensive Medicines

In a group setting, each target presentation could begin with some discussion of indications, old and new. The breadth and depth of that discussion is tailored to match the time allotted and the talents and interests of the group. In many cases the discussion could be extended to include new analogs of an old drug.

One route is presented for each target molecule in most cases. The route usually has the shortest sequence from starting materials to target molecule, is adequately described in the literature, and is likely to be close to a manufacturing route still in use today.

At first glance at the target structure, previous knowledge and experience are used to create "back of the envelope" ideas for synthesis of the target. A **text box** highlights one idea from the list which was most influential in guiding the decision-making leading to the presented route. Students should add ideas to create their own list as they work through the synthesis.

The route is presented as a retrosynthetic analysis accompanied by a brief text **Discussion**. Experimental details, references and mechanisms are not provided so that students will first focus on the structures and key disconnections. Students are then tasked to search for, evaluate, and present the procedure details (reagent(s), solvent(s), temperature, reaction time, workup, percent yield) which are the keys to the success of each reaction and the overall route. A discussion of mechanisms could accompany or follow the discussion of procedure details.

The simple sentence structure and limited vocabulary used in the text **Discussion** are intended to facilitate understanding by non-English-speaking readers. The **Discussion** includes tested online search terms (names for reactions, intermediates, and starting materials). The name used for an intermediate or starting material is the name commonly encountered in an online search. Name reactions are highlighted in **bold**. Some questions or tasks are (embedded) in the **Discussion** to draw attention to multiple options for reagent(s) for a reaction, selectivity data, or critical separation procedures.

The schemes are usually presented left-to-right without the use of retrosynthetic arrows. Retrosynthetic arrows are used to avoid confusion in some schemes. Only carbon-containing reagents, intermediates, and products are shown. One structure in a scheme often has the positions relevant to the text Discussion numbered.

The discussion is often written so that each sentence describes one reaction. This allows the discussion to be read as a description of the retrosynthesis or the synthesis. To illustrate, for amiodarone:

Retrosynthesis: The phenol is iodinated in both *ortho* positions. The phenol is formed by demethylation of the ether. The ketone is formed by acylation of 2-butyl-2,3-benzofuran with 4-methoxybenzoyl chloride (**Friedel–Crafts Acylation**). 4-Methoxybenzoyl chloride is formed from *para*-anisic acid.

Synthesis: 4-Methoxybenzoyl chloride is formed from *para*-anisic acid. The ketone is formed by acylation of 2-butyl-2,3-benzofuran with 4-methoxybenzoyl chloride (**Friedel–Crafts Acylation**). The phenol is formed by demethylation of the ether. The phenol is iodinated in both *ortho* positions.

The retrosynthetic analysis ends with specialty chemical(s), petrochemical(s), or biochemical(s) starting materials. Specialty chemical and petrochemical starting materials are highlighted with a box to direct the reader to an Appendix. **Appendix A** contains the specialty chemicals used in this workbook. One retrosynthetic analysis is provided for each specialty chemical. It is important to emphasize that specialty chemicals are often manufactured by more than one route. The preferred route often changes with the implementation of new manufacturing technologies and with changes in availability and cost of petrochemical and biochemical raw materials. Each specialty chemical retrosynthetic analysis ends with petrochemical(s) or biochemical(s) available in bulk from many suppliers. **Appendix B** lists the petrochemicals extracted or produced from coal, crude oil, or natural gas that are used in this workbook. **Appendix C** lists the biochemicals that are used in this workbook.

In the optional **Extended Discussion**, students are tasked to propose and evaluate alternative routes, reactions, or reagents encountered in their online search work.

A course based on this workbook could be organized in many ways: medicines for pain, medicines containing fluorine, medicines made using a Diels–Alder Reaction, etc. Course development will be facilitated by the provided **Indices** (name reactions, starting materials from the chiral pool, diazonium salt reactions, epoxide ring-opening reactions, fluorine-containing target molecules, furans, imidazoles, nucleophilic aromatic substitution reactions, oxidations, peptides, photochemistry, purines, pyrazines, pyridines, pyrimidines, quinolines, symmetrical molecules, thiazoles, thioethers, triazoles.)

Appendices A, B, and C and a complete list of the **References** used in preparation of the workbook are available on the companion website.

www.wiley.com/go/Harrington/routes_essential_medicine

About the Companion Website

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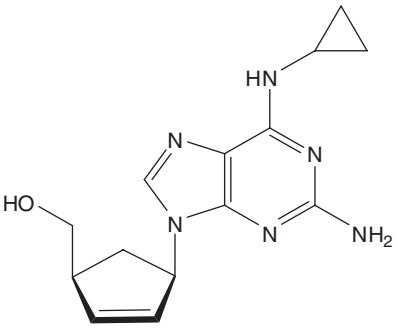
A

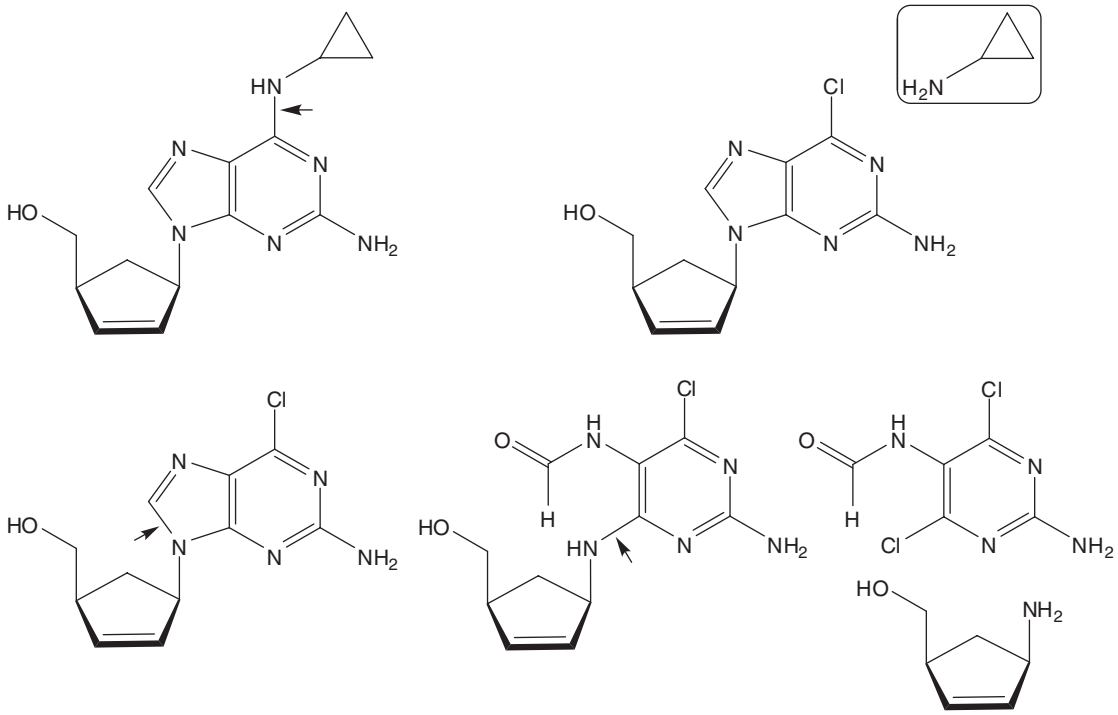
Abacavir

Antiviral Medicines/Antiretrovirals/Nucleoside or Nucleotide Reverse Transcriptase Inhibitors



When two chiral carbons are separated by one or more atoms, disconnections often lead back to an intermediate with the two chiral carbons next to each other and formed in the same reaction.

Discussion. Cyclopropanamine is introduced by chloride displacement in the final step (the chloropurine partner is also used to make the AIDS drug carbovir.) The imidazole ring of the purine is formed from the formamide (**Traube Purine Synthesis**). A C—N bond is formed by displacement of chloride from the symmetrical dichloropyrimidine by the amine of (1*S*,4*R*)-4-amino-2-cyclopentene-1-methanol.



Routes to Essential Medicines: A Workbook for Organic Synthesis, First Edition. Peter J. Harrington.

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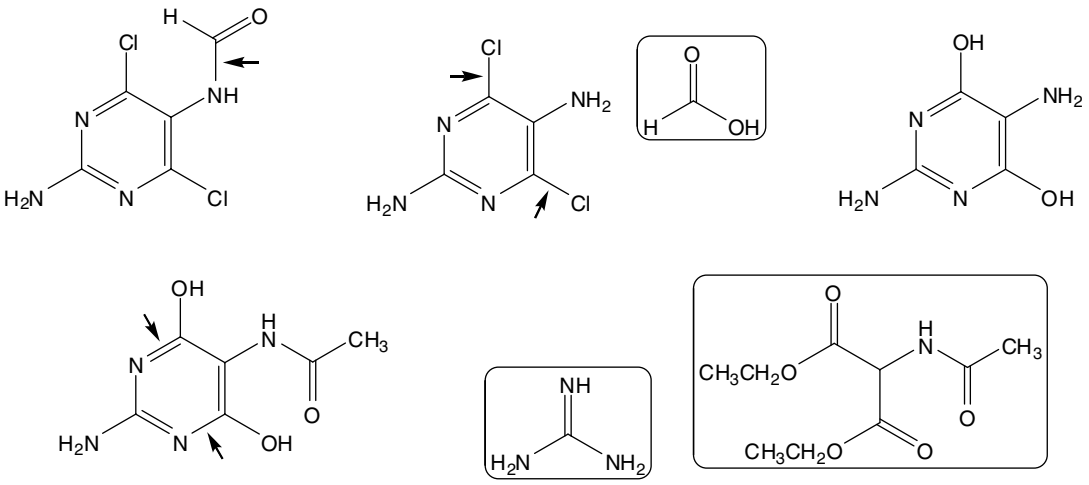
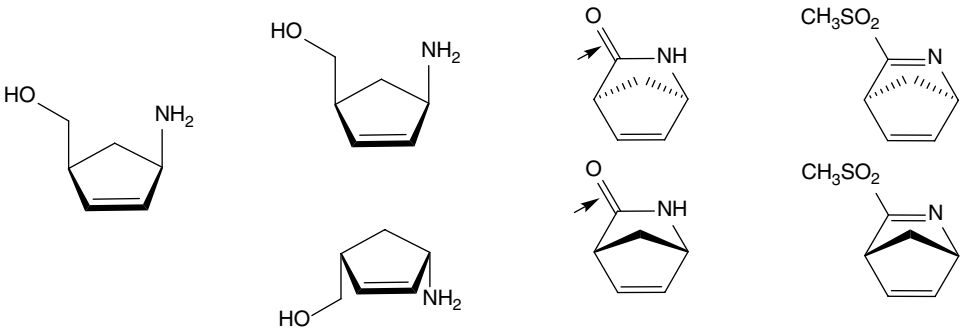
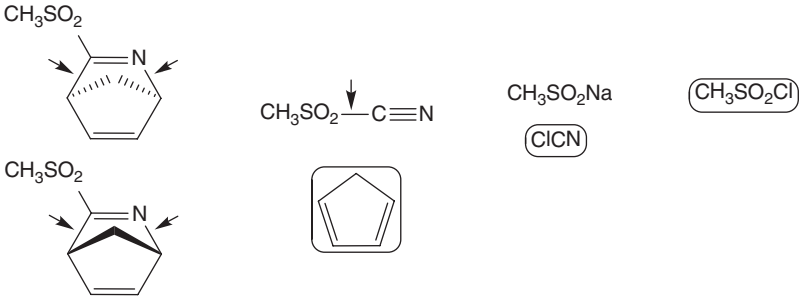
The 2,5-diaminopyrimidine 5-formamide is formed from the 2,5-diaminopyrimidine and formic acid. 2,5-Diamino-4,6-dic hloropyrimidine is formed from 2,5-diamino-4,6-dihydroxypyrimidine. 2,5-Diamino-4,6-dihydroxypyrimidine is formed by hydrolysis of the 5-acetamide. 5-Acetamido-2-amino-4,6-dihydroxypyrimidine ring is formed from guanidine and diethyl acetamidomalonate (**Pinner Pyrimidine Synthesis**).



(1*S*,4*R*)-4-Amino-2-cyclopentene-1-methanol and the (1*R*,4*S*)-enantiomer are separated by resolution. The amino alcohols are formed by reduction of the amides (**Vince Lactam**). The amides are formed by displacement of methanesulfinate by hydroxide.

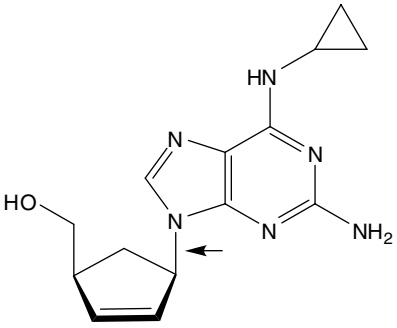


The 2-azabicyclo[2.2.1]hepta-2,5-dienes are formed by [4+2]-cycloaddition of cyclopentadiene with methanesulfonyl cyanide (**Diels–Alder Cycloaddition**). Methanesulfonyl cyanide is formed from sodium methanesulfinate and cyanogen chloride. Sodium methanesulfinate is formed by reduction of methanesulfonyl chloride.



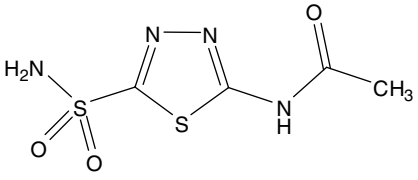
Extended Discussion

Draw the structures of the retrosynthetic analysis of one alternative route to abacavir using a disconnection of the C—N bond joining the purine ring to the cyclopentene ring. Include the structures of the retrosynthetic analysis of any organic starting material(s) from petrochemical or biochemical raw materials.



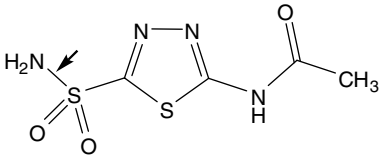
Acetazolamide

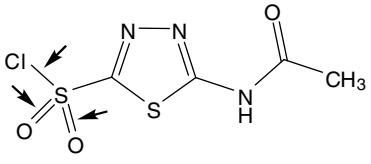
Ophthalmological Preparations/Miotics and Antiglaucoma Medicines

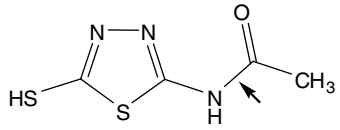


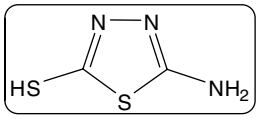
A sulfonyl chloride attached to an aromatic ring may be formed by oxidation of the thiol.

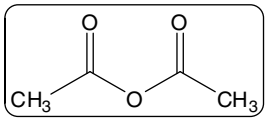
Discussion. Acetazolamide is formed in just three steps from 5-amino-1,3,4-thiadiazole-2-thiol. The sulfonamide is formed from the sulfonyl chloride in the final step. The sulfonyl chloride is formed by oxidation of the thiol. The amide is formed by acetylation of the amine using acetic anhydride.









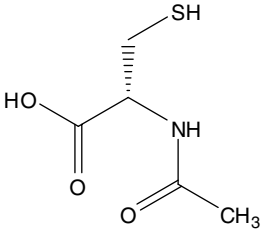


Extended Discussion

Draw the structures of the retrosynthetic analysis of one alternative route to the starting material 5-amino-1,3,4-thiadiazole-2 -thiol. List the pros for the route presented and the alternative route and select one route as the preferred route.

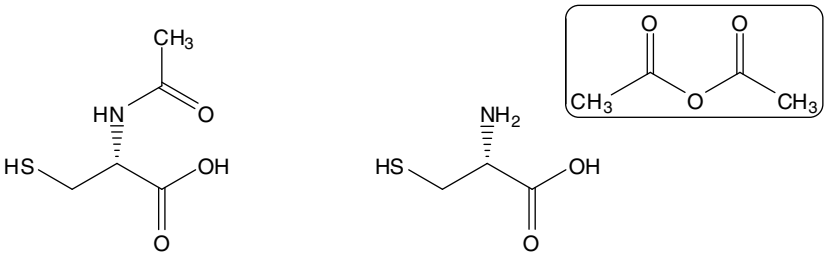
Acetylcysteine

Antidotes/Specific



A chiral carbon in a single-enantiomer molecule is often delivered in a starting material.

Discussion. *N*-Acetyl-L-cysteine is formed by acetylation of L-cysteine with acetic anhydride. L-Cysteine is produced by fermentation.

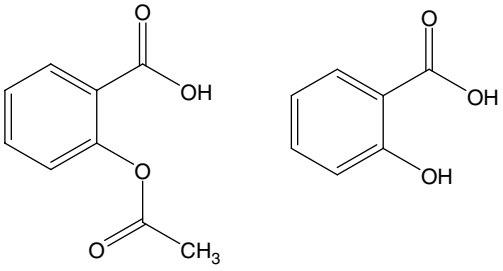


L-cysteine

Acetylsalicylic Acid

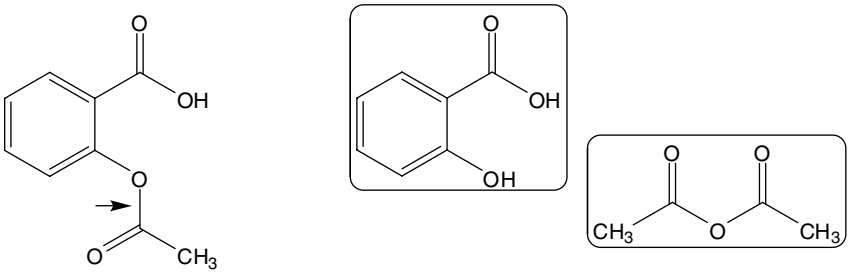
Medicines for Pain and Palliative Care/Non-Opioids and Non-Steroidal Anti-Inflammatory Medicines
Antimigraine Medicines/For Treatment of Acute Attack
Cardiovascular Medicines/Antithrombotic Medicines/Anti-Platelet Medicines
Medicines for Diseases of Joints/Juvenile Joint Diseases

salicylic acid
Dermatological Medicines/Medicines Affecting Skin Differentiation and Proliferation



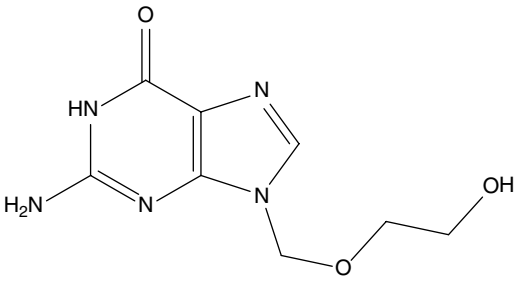
acetylsalicylic acid **salicylic acid**

Discussion. Acetylsalicylic acid (aspirin) is formed from another essential medicine, salicylic acid, and acetic anhydride. Salicylic acid is formed from phenol and carbon dioxide (**Kolbe–Schmitt Reaction**).



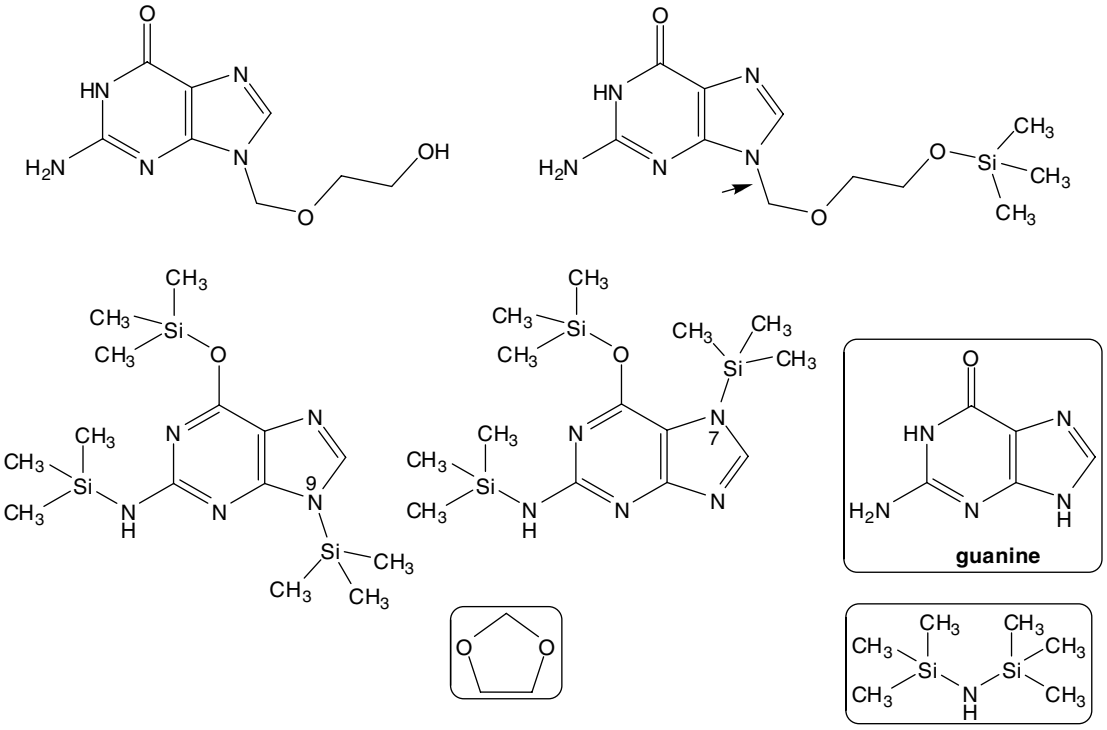
Acyclovir

Anti-Infective Medicines/Antiviral Medicines/Antiherpes Medicines
Ophthalmological Preparations/Anti-Infective Agents

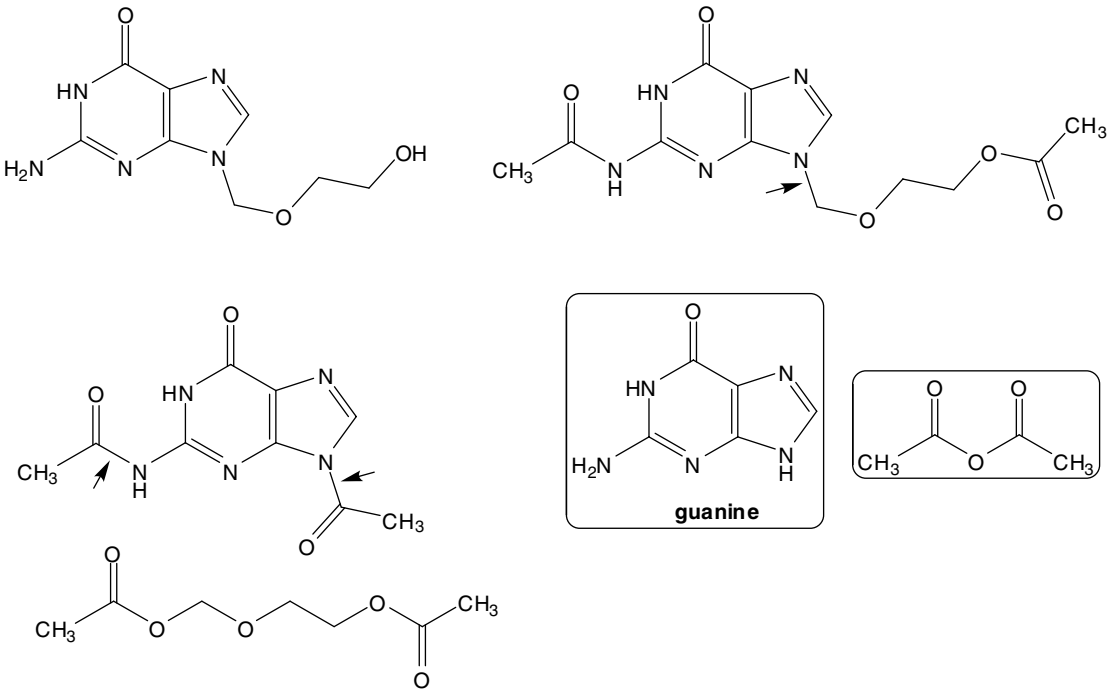


Guanine is often converted to an acylated or silylated derivative to increase solubility in organic solvents. These derivatives react with alkylating agents to form a mixture of N7-alkylated (kinetic) product and N9-alkylated (thermodynamic) product.

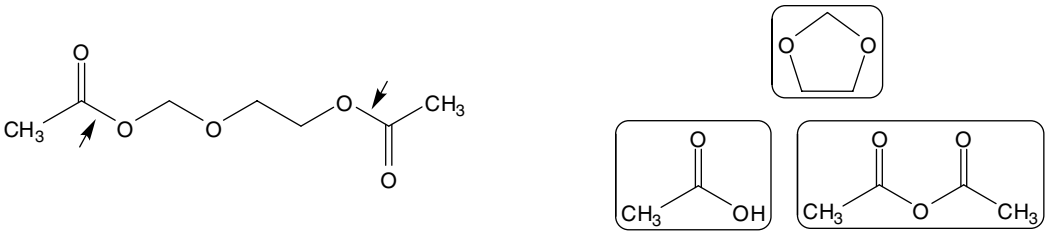
Discussion. The concepts and challenges common to the many routes to acyclovir are featured in a comparison of two preferred routes. In route A, the alcohol is released by *O*-desilylation in the final step. Acyclovir *O*-trimethylsilyl ether is formed by desilylation of persilyl acyclovir. A mixture of the N9-alkylated persilyl acyclovir and the N7-alkylated regioisomer is formed in situ by in the reaction of persilyl guanine with 1,3-dioxolane (What is the highest ratio of persilyl acyclovir to the N7-alkylated regioisomer? What reaction conditions are associated with the highest ratio? How is the N7-alkylated side product separated from the N9-alkylated product?). Persilyl guanine is a mixture of N7-TMS and N9-TMS regioisomers formed in situ by the reaction of guanine with excess hexamethyldisilazane (HMDS).



In route B, the alcohol and amino group are released by hydrolysis of the ester and amide in the final step. The alkylation of N2,9-diacetylguanine with 2-(acetoxyethoxy)methyl acetate affords a mixture of the N7- and N9-regioisomers. (Draw the structure of the N7-regioisomer. What is the highest N9:N7 ratio? What reaction conditions are associated with the highest ratio? How is the N7-alkylated side product separated from N9-alkylated product?) N2,9-Diacetylguanine is formed by reaction of guanine with acetic anhydride.



2-(Acetoxyethoxy)methyl acetate is formed from 1,3-dioxolane, acetic acid, and acetic anhydride.

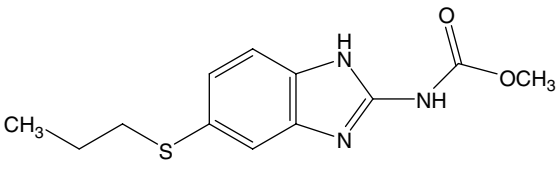


Extended Discussion

List the pros and cons for routes A and B and select one route as the preferred route.

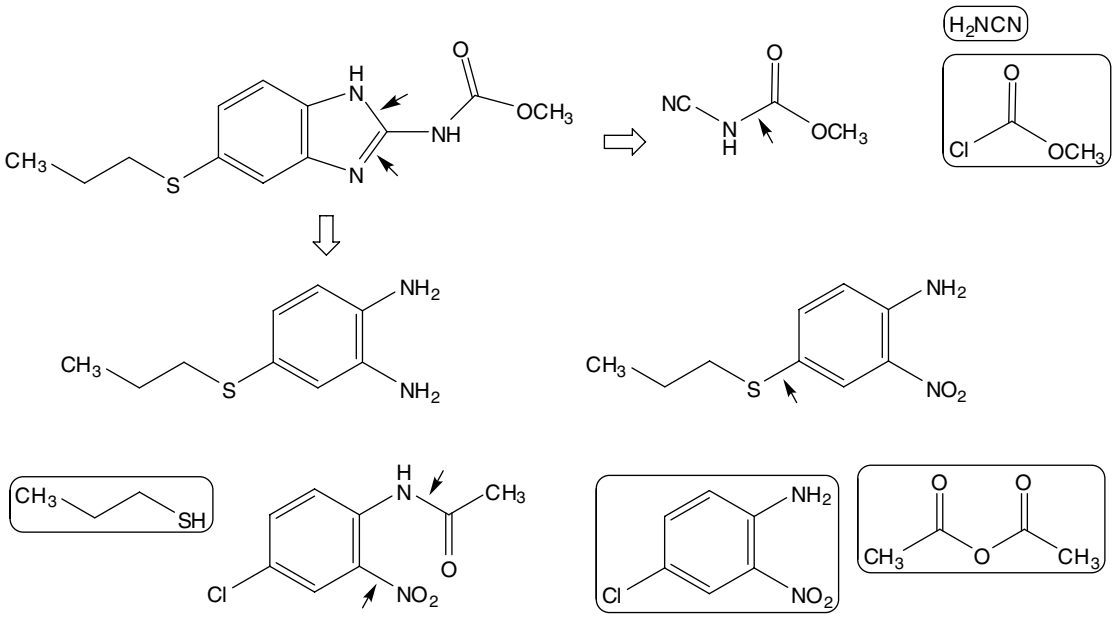
Albendazole

Anti-Infective Medicines/Anthelmintics/Antifilarials



A benzimidazole is often formed from a 1,2-phenylenediamine.

Discussion. The benzimidazole is formed in the final step from the benzene-1,2-diamine and *N*-methoxycarbonylcyanamide. *N*-Methoxycarbonylcyanamide is formed from cyanamide and methyl chloroformate. 4-(Propylthio)benzene-1,2-diamine is formed by reduction of 2-nitro-4-propylthioaniline. A C—S bond is formed by displacement of chloride from 4-chloro-2-nitroacetanilide by sodium propanethiolate. The acetanilide is also hydrolyzed under the chloride displacement reaction conditions. 4-Chloro-2-nitroacetanilide is formed from 4-chloro-2-nitroaniline and acetic anhydride.

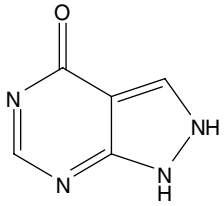


Extended Discussion

2-Nitro-4-propylthioaniline can also be manufactured from 1-chloro-2-nitrobenzene. Draw the structures of the retrosynthetic analysis of this route. List the pros and cons for both routes. Which route is preferred?

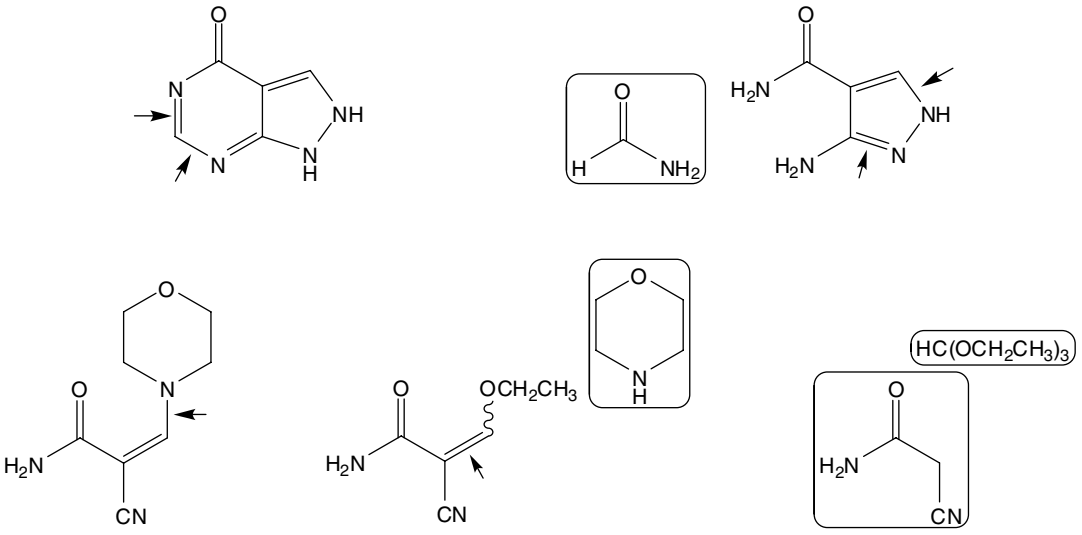
Allopurinol

Antineoplastics and Immunosuppressives/Cytotoxic and Adjuvant Medicines
Medicines for Diseases of Joints/Medicines Used to Treat Gout



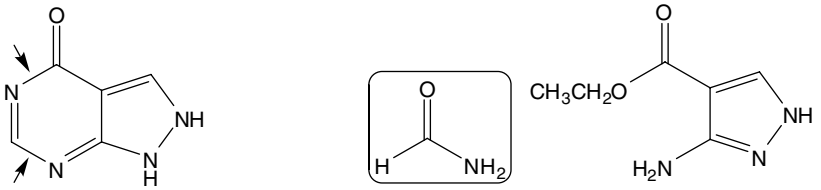
Hydrazine is often the source of the two nitrogen atoms in a pyrazole ring.

Discussion. The pyrimidine ring of the pyrazolo[3,4-d]pyrimidine is formed in the final step by reaction of 3-aminopyrazole-4-carboxamide with formamide. The pyrazole ring is formed from 2-cyano-3-morpholinoacrylamide and hydrazine. The enamine of 2-cyano-3-morpholinoacrylamide is formed from the enol ether by the displacement of ethanol by morpholine. The enol ether of 2-cyano-3-ethoxyacrylamide is formed by the reaction of 2-cyanoacetamide with triethyl orthoformate.



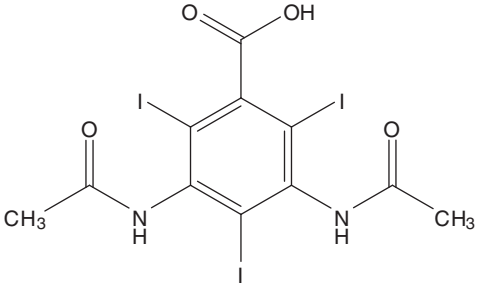
Extended Discussion

The pyrimidine ring is also formed by reaction of ethyl 3-aminopyrazole-4-carboxylate with formamide. Draw the structures of the retrosynthetic analysis of ethyl 3-aminopyrazole-4-carboxylate. List the pros and cons for both routes and select one route as the preferred route.



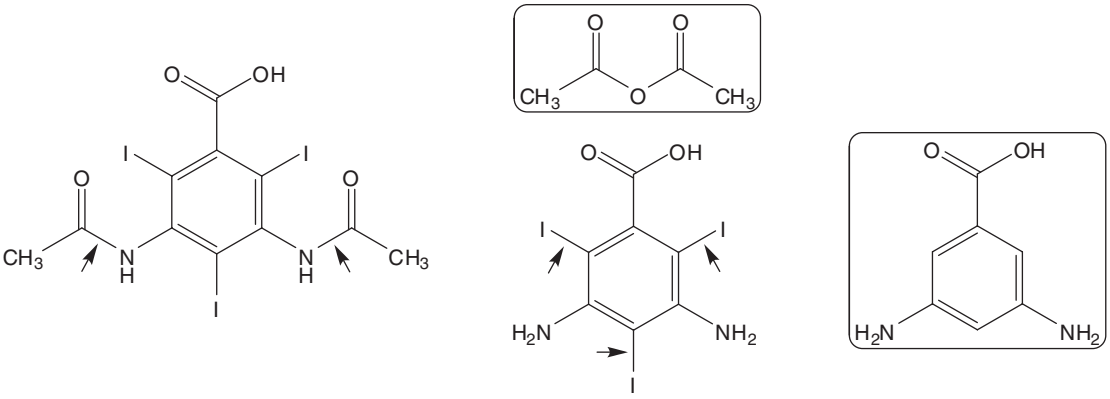
Amidotriazoate

Diagnostic Agents/Radiocontrast Media



For a symmetrical molecule, symmetrical disconnections lead back to symmetrical intermediates and are likely associated with the shortest route.

Discussion. Since some amide hydrolysis is likely under iodination conditions, the diamide is formed in the final step by reaction of the diamine with acetic anhydride. The triiodide is formed by iodination of 3,5-diaminobenzoic acid.

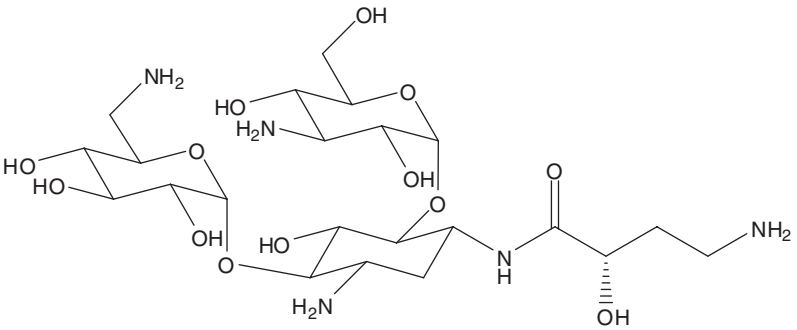


Extended Discussion

List reagents or reagent combinations used for direct iodination of an aromatic ring.

Amikacin

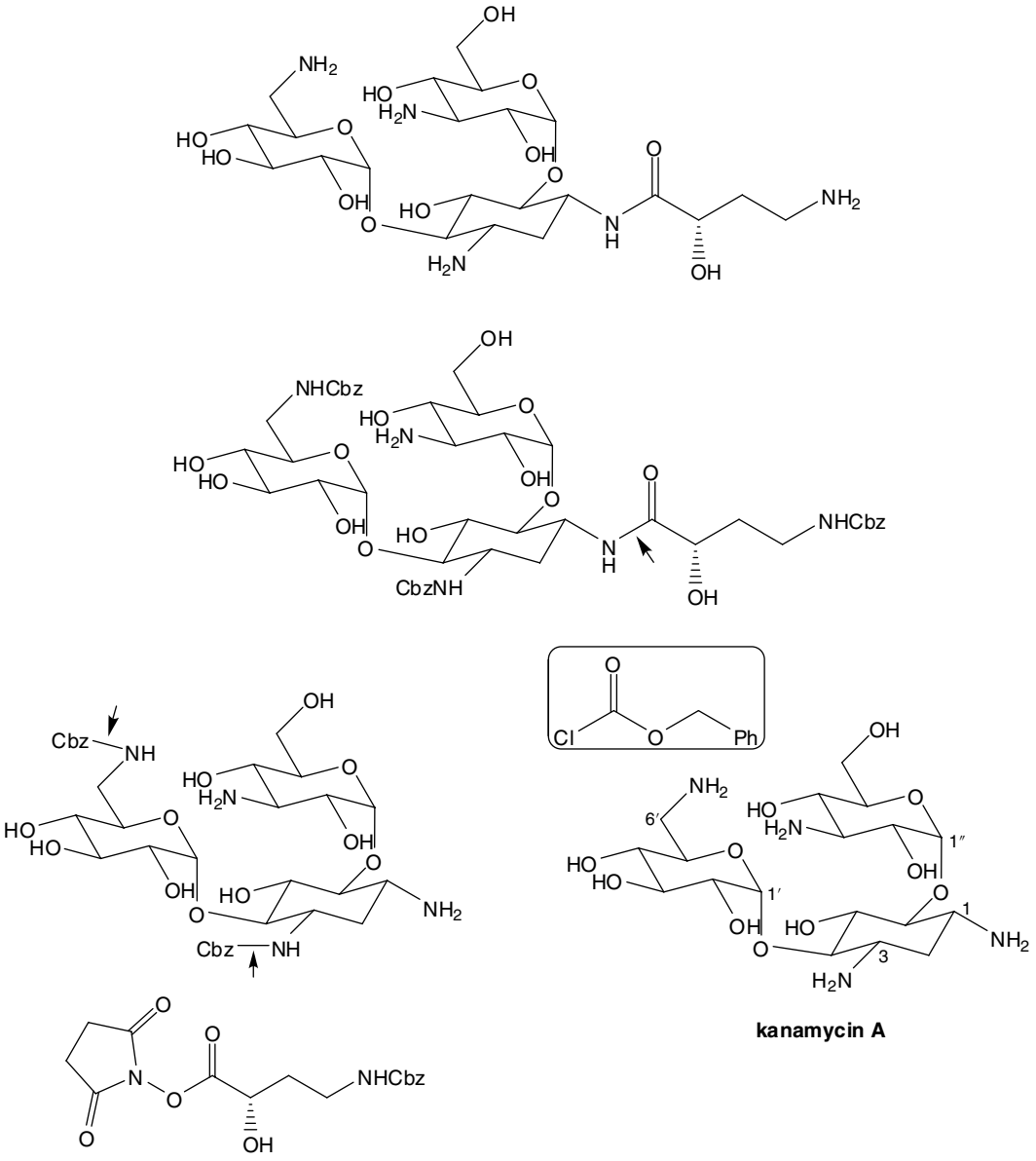
Anti-Infective Medicines/Antibacterials/Other Antibacterials
Anti-Infective Medicines/Antibacterials/Antituberculosis Medicines



A single-enantiomer molecule with multiple chiral carbons is often made by modification of a natural product which has most or all of the chiral carbons already in place.

Discussion. Amikacin is semisynthetic. Amikacin is formed by acylation of the amino group at C1 of kanamycin A. This selective acylation requires a protection–deprotection strategy since kanamycin A has four amino groups and the amino group at C1 is not the most reactive.

Three of the amino groups of amikacin are released in the final step by benzyl carbamate hydrogenolysis. The amide at C1 is formed by reaction of the amino group with an *N*-hydroxysuccinimide ester. Amino groups at C3 and C6′ of kanamycin A are protected as benzyl carbamates (Cbz). Kanamycin A is produced by fermentation.



The *N*-hydroxysuccinimide ester is formed from the carboxylic acid. The amino group of the 4-amino-2-hydroxybutanoic acid is protected as the benzyl carbamate. (*S*)-4-Amino-2-hydroxybutanoic acid is formed from (S)-2-hydroxyglutaramic acid (**Hofmann Rearrangement**). The amide is formed from the lactone. (*S*)-5-Oxotetrahydrofuran-2-carboxylic acid lactone is formed by diazotization of L-glutamic acid. L-Glutamic acid is produced by fermentation.