THE ORGANIC CHEMISTRY OF DRUG SYNTHESIS

Volume 7

DANIEL LEDNICER
North Bethesda, MD

WILEY-INTERSCIENCE
A JOHN WILEY & SONS, INC., PUBLICATION

THE ORGANIC CHEMISTRY OF DRUG SYNTHESIS

THE WILEY BICENTENNIAL–KNOWLEDGE FOR GENERATIONS

Each generation has its unique needs and aspirations. When Charles Wiley first opened his small printing shop in lower Manhattan in 1807, it was a generation of boundless potential searching for an identity. And we were there, helping to define a new American literary tradition. Over half a century later, in the midst of the Second Industrial Revolution, it was a generation focused on building the future. Once again, we were there, supplying the critical scientific, technical, and engineering knowledge that helped frame the world. Throughout the 20th Century, and into the new millennium, nations began to reach out beyond their own borders and a new international community was born. Wiley was there, expanding its operations around the world to enable a global exchange of ideas, opinions, and know-how.

For 200 years, Wiley has been an integral part of each generation's journey, enabling the flow of information and understanding necessary to meet their needs and fulfill their aspirations. Today, bold new technologies are changing the way we live and learn. Wiley will be there, providing you the must-have knowledge you need to imagine new worlds, new possibilities, and new opportunities.

Generations come and go, but you can always count on Wiley to provide you the knowledge you need, when and where you need it!

William J. Pesce

WILLIAM J. PESCE
PRESIDENT AND CHIEF EXECUTIVE OFFICER

Peter Booth Wiley

PETER BOOTH WILEY
CHAIRMAN OF THE BOARD

THE ORGANIC CHEMISTRY OF DRUG SYNTHESIS

Volume 7

DANIEL LEDNICER
North Bethesda, MD

WILEY-INTERSCIENCE
A JOHN WILEY & SONS, INC., PUBLICATION

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

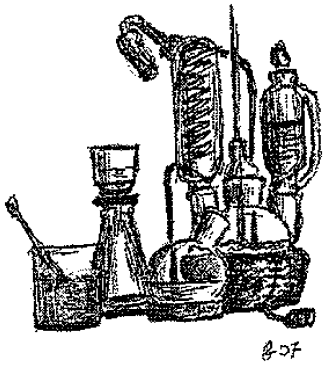
Library of Congress Cataloging-in-publication Data is available.

ISBN 978-0-470-10750-8

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

To the memory of I. Moyer Hunsberger and Melvin S. Newman
who set me on course. . .



CONTENTS

PREFACE

The first volume of *The Organic Chemistry of Drug Synthesis* was originally visualized as a single free-standing book that outlined the syntheses of most drugs that had been assigned non-proprietary names in 1975 at the time the book was written. Within a year or so of publication in 1977, it had become evident that a good many drugs had been overlooked. That and the encouraging reception of the original book led to the preparation of a second volume. That second book not only made up for the lacunae in the original volume but also covered additional new drug entities as well. With that second volume assignment of non-proprietary names by USAN became the criterion for inclusion. That book, published in 1980, thus included in addition all agents that had been granted USAN since 1976. What had been conceived as a single book at this point became a series. The roughly 200 new USAN coined every five years over the next few decades turned out to nicely fit a new volume in the series. This then dictated the frequency for issuing new compendia. After the most recent book in the series, *Volume 6*, was published in 1999, it became apparent that a real decline in the number of new drug entities assigned non-proprietary names had set in. The customary half-decade interval between books was apparently no longer appropriate.

A detailed examination of the 2005 edition of the *USAN Dictionary of Drug Names* turned up 220 new non-proprietary names that had been assigned since the appearance of Volume 6. Many of these compounds represent quite novel structural types first identified by sophisticated new

cell-based assays. This clearly indicated the need for the present volume in the series *The Organic Chemistry of Drug Synthesis*.

This new book follows the same format as the preceding volumes. Compounds are classed by their chemical structures rather than by their biological activities. This is occasionally awkward since compounds with the same biological activity but significantly different structures are relegated to different chapters, a circumstance particularly evident with estrogen antagonists that appear in three different chapters. The cross index found at the end of the book, it is hoped, partly overcomes this problem. The syntheses are discussed from an organic chemist's point of view, accompanied by the liberal use of flow diagrams. As was the case in the preceding volumes, a thumbnail explanation of the biological activity of each new compound precedes the discussion of its biological activity.

Several trends in the direction of drug discovery research seemed to emerge during the preparation of this book. Most of the preceding volumes included one or more therapeutic classes populated by many structurally related potential drugs. *Volume 6* for example described no fewer than a half dozen HIV-protease inhibitors and a similar number of the "triptan" drugs aimed at treating migraine. The distribution of therapeutic activities in the present volume is quite distinct from that found in the earlier books. This new set, for example, includes a sizeable number of antineoplastic and antiviral agents. These two categories together in fact account for just over one third of the compounds in the present volume. The antitumor candidates are further distinct in that specific agents act against very specific tumor-related biological end points. This circumstance combined with mechanism based design in other disease areas probably reflect the widespread adoption of in-vitro screening in the majority of pharmaceutical research laboratories.

The use of combinatorial chemistry for generating libraries to feed in-vitro screens has also become very prevalent over the past decade. This book is silent on that topic since compounds are only included when in a quite advanced developmental stage. Some of the structures that include strings of unlikely moieties suggest that those compounds may have been originally prepared by some combinatorial process.

The internet has played a major role in finding the articles and patents that were required to put this account together. The NIH-based website PubChem was an essential resource for finding structures of compounds that appear in this book; hits more often than not include CAS Registry Numbers. References to papers on the synthesis of compounds could sometimes be found with the other NIH source PubMed. The ubiquitous Google was also quite helpful for finding sources for syntheses. In some

of the earlier volumes, references to patents were accompanied by references to the corresponding CAS abstract since it was often difficult to access patents. The availability of actual images of all patents from either the U.S. patent office (www.uspto.gov) or those from European elsewhere (http://ep.espacenet.com) has turned the situation around. There was always the rather pricey STN online when all else failed.

This volume, like its predecessors, is aimed at practicing medicinal and organic chemists as well as graduate and advanced undergraduate students in organic and medicinal chemistry. The book assumes a good working knowledge of synthetic organic chemistry and some exposure to modern biology.

As a final note, I would like to express my appreciation to the staff of the library in Building 10 of the National Institutes of Health. Not only were they friendly and courteous but they went overboard in fulfilling requests that went well beyond their job descriptions.

CHAPTER 1

OPEN-CHAIN COMPOUNDS

Carbocyclic or heterocyclic ring systems comprise the core of chemical structures of the vast majority of therapeutic agents. This finding results in the majority of drugs exerting their effect by their actions at receptor or receptor-like sites on cells, enzymes, or related entities. These interactions depend on the receiving site being presented with a molecule that has a well-defined shape, distribution of electron density, and array of ionic or ionizable sites, which complement features on the receptor. These requirements are readily met by the relatively rigid carbocyclic or heterocyclic molecules. A number of important drugs cannot, however, be assigned to one of those structural categories. Most of these agents act as false substrates for enzymes that handle peptides. The central structural feature of these compounds is an open-chain sequence that mimics a corresponding feature in the normal peptide. Although these drugs often contain carbocyclic or heterocyclic rings in their structures, these features are peripheral to their mode of action. Chapter 1 concludes with a few compounds that act by miscellany and mechanisms and whose structures do not fit other classifications.

The Organic Chemistry of Drug Synthesis, Volume 7. By Daniel Lednicer

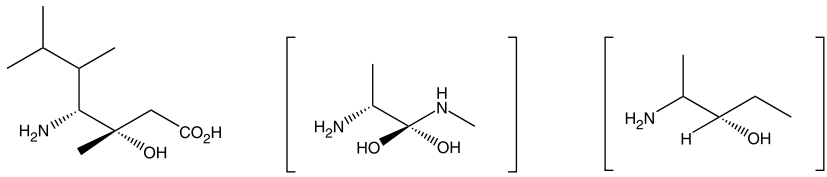
1. PEPTIDOMIMETIC COMPOUNDS

A. Antiviral Protease Inhibitors

1. Human Immunodeficiency Virus. The recognition of acquired immune deficiency syndrome (AIDS) in the early 1980s and the subsequent explosion of what had seemed at first to be a relatively rare disease into a major worldwide epidemic, lent renewed emphasis to the study of virus-caused disease. Treatment of viral disease is made particularly difficult by the fact that the causative organism, the virion, does not in the exact meaning of the word, replicate. Instead, it captures the reproductive mechanism of infected cells and causes those to produce more virions. Antiviral therapy thus relies on seeking out processes that are vital for producing those new infective particles. The first drugs for treating human immunodeficiency virus (HIV) infection comprised heterocyclic bases that interfered with viral replication by interrupting the transcription of viral ribonucleic acid (RNA) into the deoxyribonucleic acid (DNA) required by the host cell for production of new virions. The relatively fast development of viral strains resistant to these compounds has proven to be a major drawback to the use of these reverse transcriptase inhibitors. The drugs do, however, still form an important constituent in the so-called cocktails used to treat AIDS patients. Some current reverse transcriptase inhibitors are described in Chapters 4 and 6. The intense focus on the HIV virus revealed yet another point at which the disease may be tackled. Like most viruses, HIV comprises a packet of genetic material, in this case RNA, encased in a protein coat. This protein coat provides not only protection from the environment, but also includes peptides that recognize features on host cells that cause the virion to bind to the cell and a few enzymes crucial for replication. Many normal physiological peptides are often elaborated as a part of a much larger protein. Specialized peptidase enzymes are required to cut out the relevant protein. This proved to be the case with the peptides required for forming the envelopes for newly generated virions. Compounds that inhibit the scission of the protein elaborated by the infected host, the HIV protease inhibitors, have provided a valuable set of drugs for treatment of infected patients. The synthesis of four of those drugs were outlined in Volume 6 of this series. Work on compounds in this class has continued apace as evidenced by the half dozen new protease inhibitors that have been granted nonproprietary names since then.

As noted in Volume 6, the development of these agents was greatly facilitated by a discovery in a seemingly unrelated area. Research aimed

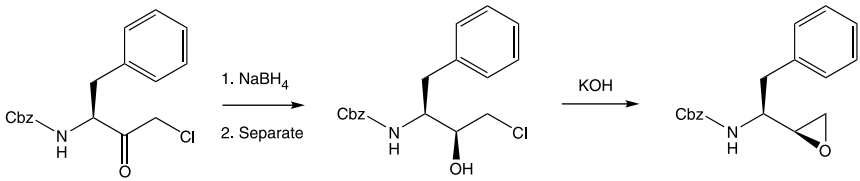
at development of renin inhibitors as potential antihypertensive agents had led to the discovery of compounds that blocked the action of this peptide cleaving enzyme. The amino acid sequence cleaved by renin was found to be fortuitously the same as that required to produce the HIV peptide coat. Structure–activity studies on renin inhibitors proved to be of great value for developing HIV protease inhibitors. Incorporation of an amino alcohol moiety proved crucial to inhibitory activity for many of these agents. This unit is closely related to the one found in the statine, an unusual amino acid that forms part of the pepstatin, a fermentation product that inhibits protease enzymes.



Statine | Transition State | Protease Inhibitor Fragment

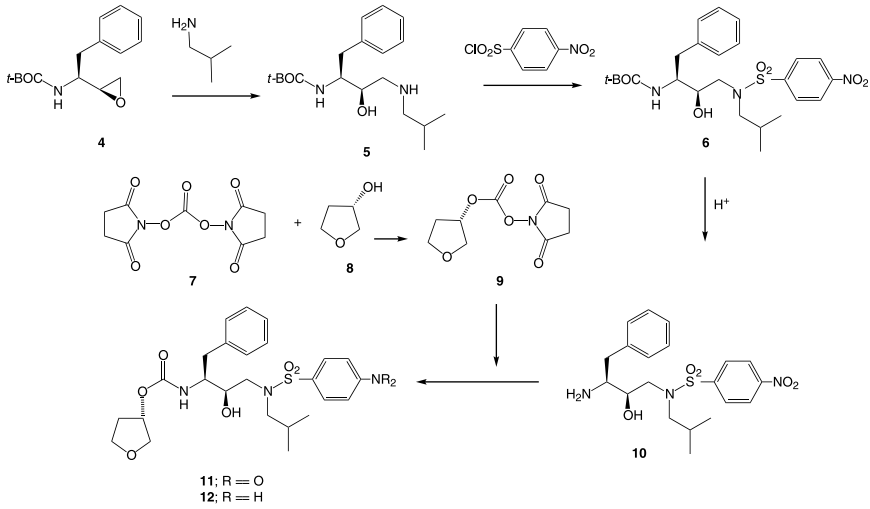
This moiety may be viewed as a carbon analogue of the transition state in peptide cleavage. The fragment is apparently close enough in structure to such an intermediate as to fit the cleavage site in peptidase enzymes. Once bound, this inactivates the enzyme as it lacks the scissile carbon–nitrogen bond. All five newer HIV protease inhibitors incorporate this structural unit.

One scheme for preparing a key intermediate for incorporating that fragment begins with the chloromethyl ketone (**1**) derived from phenylalanine, in which the amine is protected as a carbobenzyloxy (Cbz) group. Reduction of the carbonyl group by means of borohydride affords a mixture of aminoalcohols. The major syn isomer **2** is then isolated. Treatment of **2** with base leads to internal displacement of halogen and formation of the epoxide (**3**).[1]



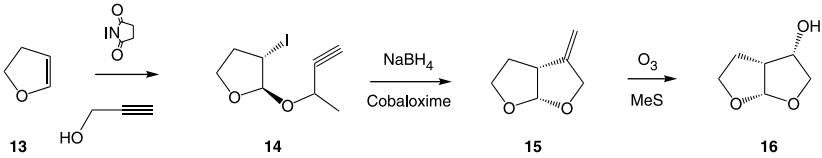
1 **2** **3**

The corresponding analogue (**4**) in which the amine is protected as a *tert*-butyloxycarbonyl function (*t*-BOC) comprises the starting material for the HIV protease inhibitor **amprenavir** (**12**). Reaction of **4** with isobutyl amine leads to ring opening of the oxirane and formation of the aminoalcohol (**5**). The thus-formed secondary amine in the product is converted to the sulfonamide (**6**) by exposure to *p*-nitrobenzenesulfonyl chloride. The *t*-BOC protecting group is then removed by exposure to acid leading to the primary amine (**10**). In a convergent scheme, chiral 3-hydroxytetrahydrofuran (**8**) is allowed to react with bis(*N*-succinimidooxy)carbonate (**7**). The hydroxyl displaces one of the *N*-hydroxysuccinimide groups to afford the tetrahydrofuran (THF) derivative (**9**) equipped with a highly activated leaving group. Reaction of this intermediate with amine 10 leads to displacement of the remaining *N*-hydroxysuccinimide and incorporation of the tetrahydrofuryl moiety as a urethane (**11**). Reduction of the nitro group then affords the protease inhibitor (**12**).[2]

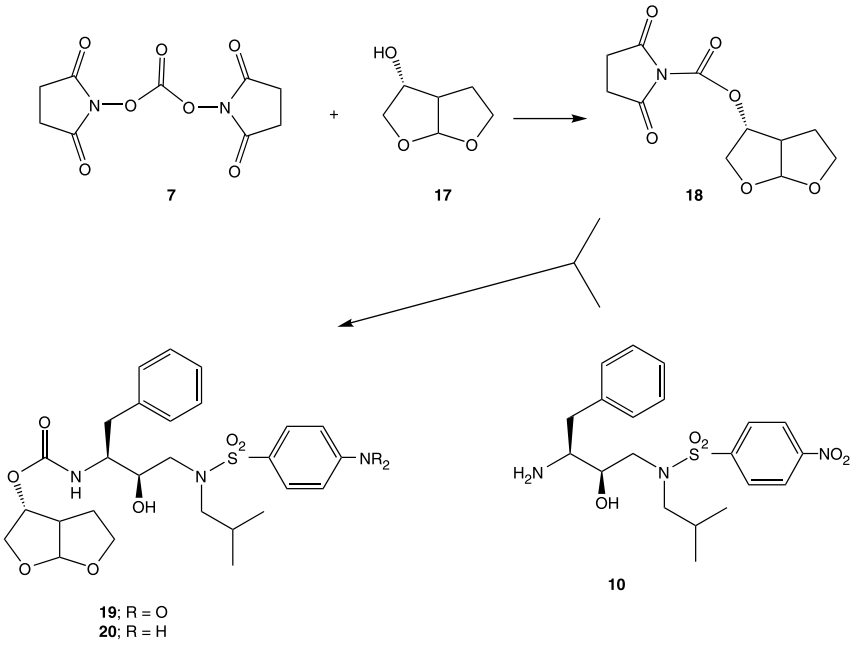


Much the same sequence leads to a protease inhibitor that incorporates a somewhat more complex furyl function-linked oxygen heterocyclic. This fused bis(tetrahydrofuryl) alcohol (**16**) was designed to better interact with a pocket on the viral protease. The first step in preparing this intermediate consists of reaction of dihydrofuran (**13**) with propargyl alcohol and iodosuccinimide to afford the iodoether (**14**). Free radical displacement of the iodine catalyzed by cobaloxime leads to the fused

perhydrofuranofuran (**15**). The exomethylene group in the product is then cleaved by means of ozone; reductive workup of the ozonide leads to racemic **16**. The optically pure single entity (**17**) is then obtained by resolution of the initial mixture of isomers with immobilized lipase.[3]

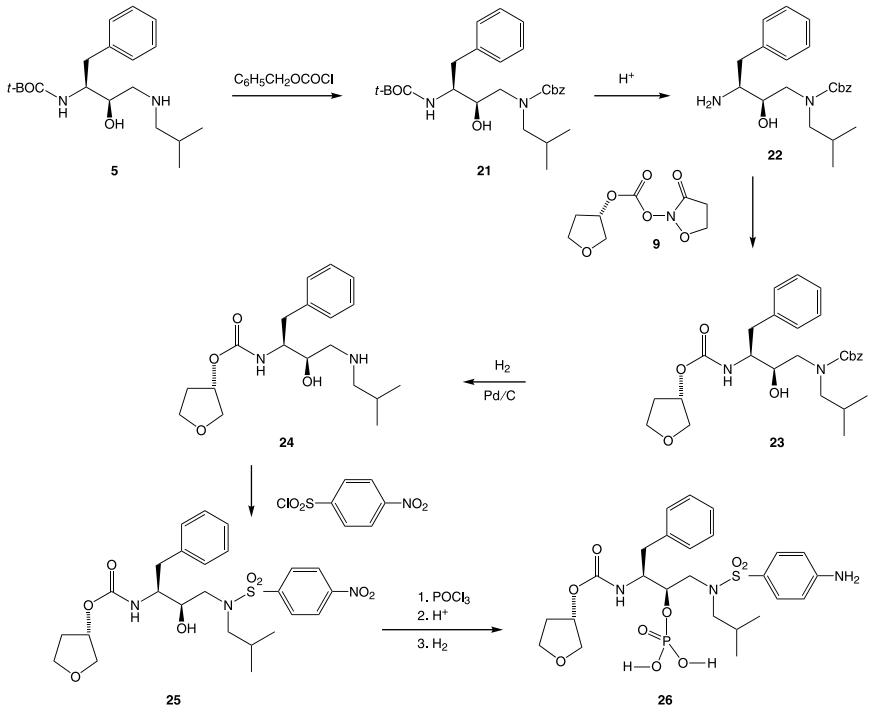


That product (**17**) is then converted to the activated *N*-hydoxysuccinimide derivative **18** as in the case of the monocyclic furan. Reaction with the primary amine **10** used to prepare amprenavir then leads to the urethane (**19**). Reduction of the nitro group then affords **darunavir**[4] (**20**).



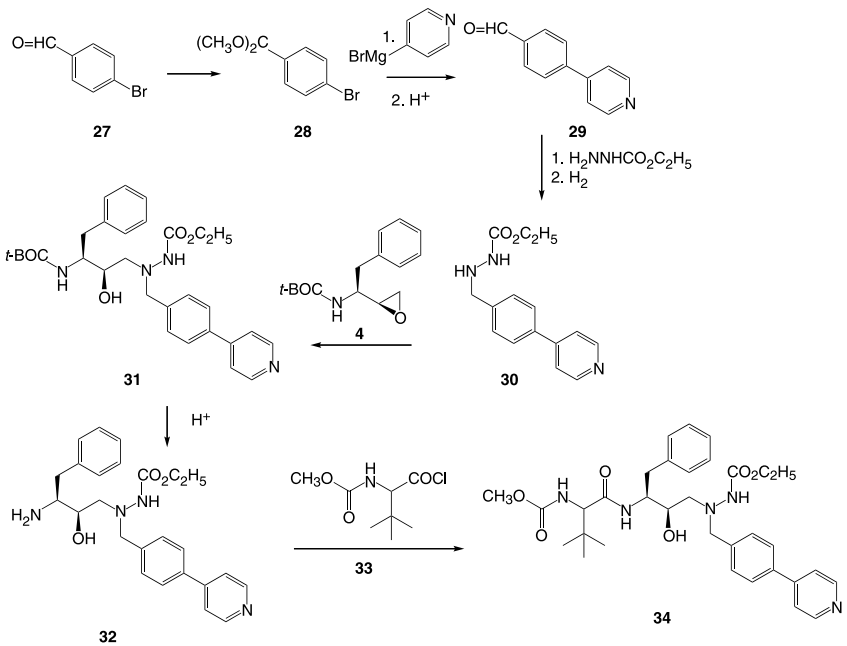
The synthesis of the amprenavir derivative, which is equipped with a solubilizing phosphate group, takes a slightly different course from that used for the prototype. The protected intermediate **5** used in the synthesis of **12** is allowed to react with benzyloxycarbonyl chloride to provide the

doubly protected derivative **21**, a compound that bears a *t*-BOC group on one nitrogen and a Cbz grouping on the other. Exposure to acid serves to remove the *t*-BOC group, affording the primary amine **22**. This compound is then condensed with the activated intermediate **9** used in the preparation of the prototype to yield the urethane **23**. Catalytic hydrogenation then removes the remaining protecting group to give the secondary amine **24**. Reaction as before with *p*-nitrobenzenesulfonyl chloride gives the sulfonamide **25**. This intermediate is allowed to react with phosphorus oxychloride under carefully controlled conditions. Treatment with aqueous acid followed by a second catalytic hydrogenation affords the water soluble protease inhibitor **fosamprenavir** (**26**).[5]



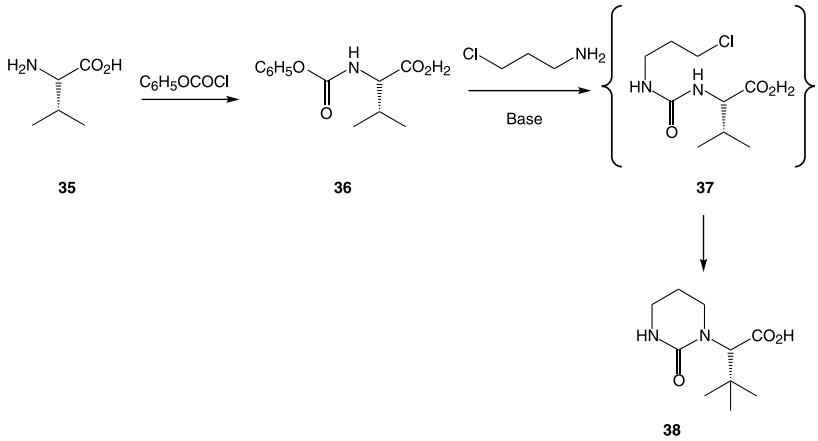
The preceding three antiviral agents tend to differ form each other by only relatively small structural details. The next protease inhibitor includes some significant structural differences though it shares a similar central aminoalcohol sequence that is presumably responsible for its activity. Construction of one end of the molecule begins with protection of the carbonyl function in *p*-bromobenzaldehyde (**27**) as its methyl acetal (**28**) by treatment with methanol in the presence of acid. Reaction of that intermediate with the Grignard reagent from 4-bromopyridine leads to unusual

displacement of bromine from the protected benzaldehyde and formation of the coupling product. Mild aqueous acid restores the aldehyde function to afford **29**. This compound is then condensed with carbethoxy hydrazine to form the respective hydrazone; reduction of the imine function leads to the substituted hydrazine (**30**). Reaction of **30** with the by-now familiar amino-epoxide (**4**) results in oxirane opening by attack of the basic nitrogen in the hydrazine (**30**) and consequent formation of the addition product **31**. The *t*-BOC protecting group is then removed by treatment with acid. The final step comprises acylation of the free primary amine in **32** with the acid chloride from the *O*-methyl urethane (**33**). This last compound (**32**) is a protected version of an unnatural α-aminoacid that can be viewed as valine in with an additional methyl group on what had been the side-chain secondary carbon atom. Thus, the protease inhibitor **atazanavir** (**34**) is obtained.[6]



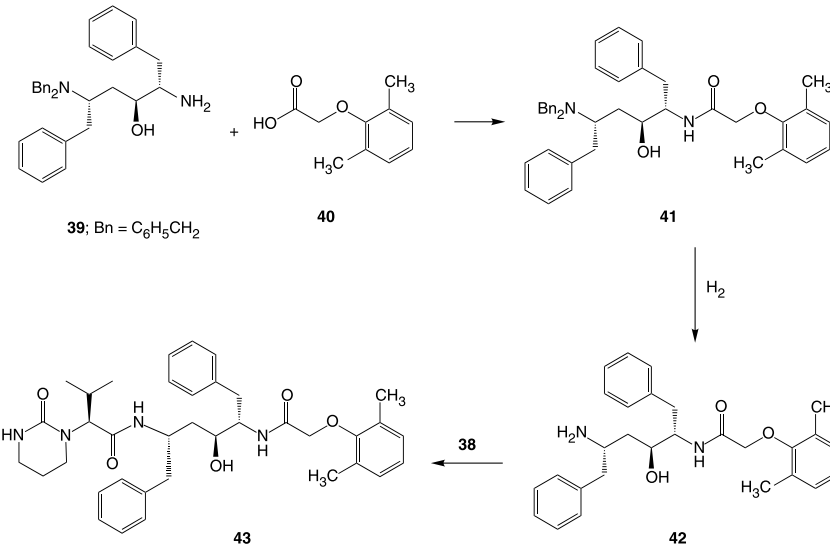
A terminal cyclic urea derivative of valine is present at one terminus in **lopinavir** (**43**). Preparation of this heterocyclic moiety begins with conversion of valine (**35**) to its phenoxycarbonyl derivative by reaction with the corresponding acid chloride. Alkylation of the amide nitrogen with 3-chloropropylamine in the presence of base under very carefully controlled pH results in displacement of the phenoxide group to give the

urea intermediate (**37**). This compound then spontaneously undergoes internal displacement of chlorine to form the desired derivative (**38**).



35 **36** **37** **38**

The statine-like aminoalcohol function in this compound differs from previous examples by the presence of an additional pendant benzyl group; the supporting carbon chain is of necessity longer by one member. Condensation of that diamine (**39**),[7] protected at one end as its *N*,*N*-dibenzyl derivative, with 2,6-dimethylphenoxyacetic acid (**40**) gives the corresponding amide (**41**). Hydrogenolysis then removes the benzyl protecting groups to afford primary amine **42**. Condensation of that with intermediate **34** affords the HIV protease inhibitor **43**.[8]

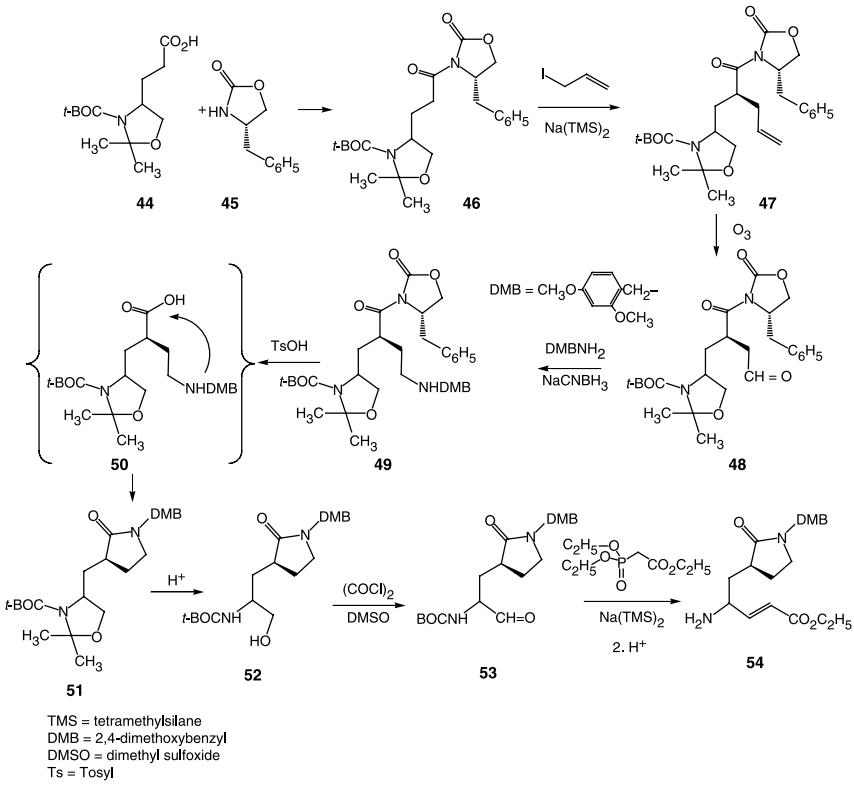


39; Bn = $C_6H_5CH_2$ **40** **41** **42** **43**

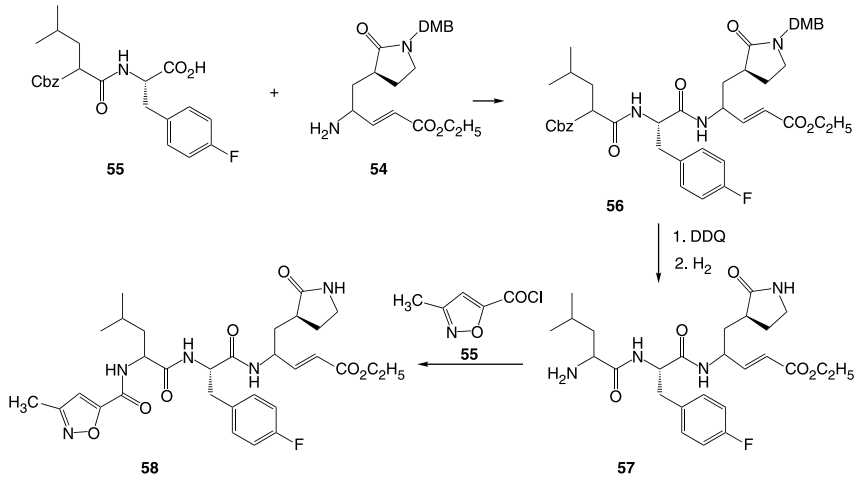
2. Human Rhinovirus. Human rhinoviruses are one of the most frequent causes of that affliction that accompanies cooling weather, the common cold. This virus also consists of a small strand of RNA enveloped in a peptide coat. Expression of fresh virions in this case depends on provision of the proper peptide by the infected host cell. That in turn hinges on excision of that peptide from the larger initially produced protein. Protease inhibitors have thus been investigated as drugs for treating rhinovirus infections. The statine-based HIV drugs act by occupying the scission site of the protease enzyme and consequently preventing access by the HIV-related substrate. That binding is, however, reversible in the absence of the formation of a covalent bond between drug and enzyme. A different strategy was employed in the research that led to the rhinovirus protease inhibitor **rupinavir** (**58**). The molecule as a whole is again designed to fit the protease enzyme, as in the case of the anti-HIV compounds. In contrast to the latter compound, however, this agent incorporates a moiety that will form a covalent bond with the enzyme, in effect inactivating it with finality. The evocative term "suicide inhibitor" has sometimes been used for this approach since both the substrate and drug are destroyed.

The main part of the somewhat lengthy convergent synthesis consists of the construction of the fragment that will form the covalent bond with the enzyme. The unsaturated ester in this moiety was designed to act as a Michael acceptor for a thiol group on a cysteine residue known to be present at the active site. The preparation of that key fragment starts with the protected form of chiral 3-amino-4-hydroxybutyric acid (**44**); note that the oxazolidine protecting group simply comprises a cyclic hemiaminal of the aminoalcohol with acetone. The first step involves incorporation of a chiral auxiliary to guide introduction of an additional carbon atom. The carboxylic acid is thus converted to the corresponding acid chloride and that reacted with the (*S*)-isomer of the by-now classic oxazolidinone (**45**) to give derivative **46**. Alkylation of the enolate from **46** with allyl iodide gives the corresponding allyl derivative (**47**) as a single enantiomer. The double bond is then cleaved with ozone; reductive workup of the ozonide affords the aldehyde (**48**). Reductive amination of the carbonyl group with 2,6-dimethoxybenzylamine in the presence of cyanoborohydride proceeds to the corresponding amine **49**. This last step in effect introduced a protected primary amino group at that position. The chiral auxiliary grouping is next removed by mild hydrolysis. The initially formed amino acid (**50**) then cyclizes to give the five-membered lactam (**51**). Treatment under stronger hydrolytic conditions subsequently serves to open the cyclic hemiaminal grouping to reveal the free aminoalcohol

(**52**). Swern-type oxidation of the terminal hydroxyl group in this last intermediate affords an intermediate (**53**) that now incorporates the aldehyde group required for building the Michael acceptor function. Thus reaction of that compound with the ylide from ethyl 2-diethoxyphosphonoacetate adds two carbon atoms and yields the acrylic ester (**54**).



The remaining portion of the molecule is prepared by the condensation of *N*-carbobenzyloxyleucine with *p*-fluorophenylalanine to yield the protected dipeptide (**55**). Condensation of that intermediate with the Michael acceptor fragment (**54**) under standard peptide-forming conditions leads to the tripeptide-like compound (**53**). Reaction of **53** with dichlorodicyanoquinone (DDQ) leads to unmasking of the primary amino group at the end of the chain by oxidative loss of the DMB protecting group. Acylation of that function with isoxazole (**55**) finally affords the rhinovirus protease inhibitor rupinavir (**58**).[9]

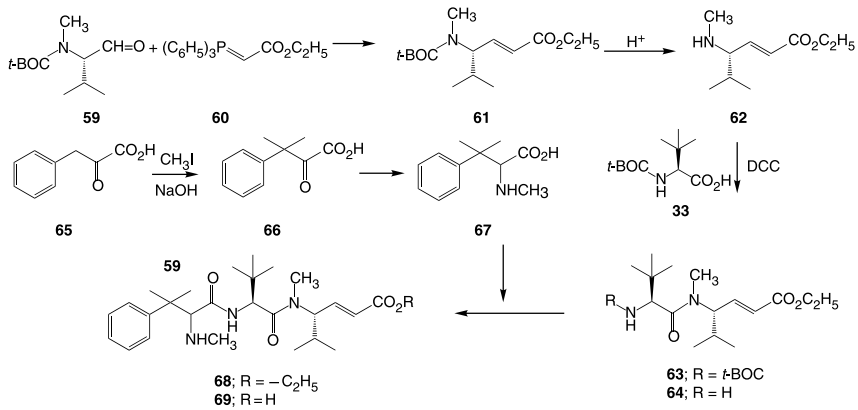


2. MISCELLANEOUS PEPTIDOMIMETIC COMPOUNDS

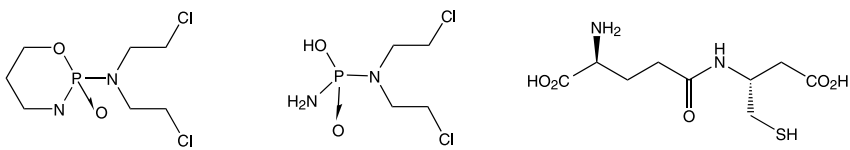
Polymers of the peptide tubulin make up the microtubules that form the microskeleton of cells. Additionally, during cell division these filaments pull apart the nascent newly formed pair of nuclei. Compounds that interfere with tubulin function and thus block this process have provided some valuable antitumor compounds. The vinca alkaloid drugs vincristine and vinblastine, for example, block the self-assembly of tubulin into those filaments. Paclitaxel, more familiarly known as Taxol, interestingly stabilizes tubulin and in effect freezes cells into mid-division. Screening of marine natural products uncovered the cytotoxic tripeptide-like compound hemiasterlin, which owed its activity to inhibition of tubulin. A synthetic program based on that lead led to the identification of **taltobulin** (**69**), an antitumor compound composed, like its model, of sterically crowded aminoacid analogues. The presence of the nucleophile-accepting acrylate moiety recalls **58**.

One arm of the convergent synthesis begins with the construction of that acrylate-containing moiety. Thus, condensation of the *t*-BOC protected α-aminoaldehyde derived from valine with the carbethoxymethylene phosporane (**60**) gives the corresponding chain extended amino ester (**61**). Exposure to acid serves to remove the protecting group to reveal the primary amine (**62**). Condensation of that intermediate with the tertiary butyl-substituted aminoacid **33**, used in a previous example leads to the protected amide (**63**); the *t*-BOC group in this is again removed with acid unmasking the primary amino group in **64**. Construction of the other major fragment first involves addition of a pair of methyl groups

to the benzylic position of pyruvate (**65**). This transform is accomplished under surprisingly mild conditions by simply treating the ketoacid with methyl iodide in the presence of hydroxide. Treatment of product **66** with methylamine and diborane results in reductive amination of the carbonyl group, and thus formation of α-aminoacid **67** as a mixture of the two isomers. Condensation of that with the dipeptide-like moiety **64** under standard peptide-forming conditions gives the amide **68** as a mixture of diastereomers. The isomers are then separated by chromatography; saponification of the terminal ester function of the desired (*SSS*)-isomer affords the antitumor agent taltobulin (**69**).[10]



The alkylating agent cyclophosphamide is one of the oldest U.S. Food and Drug Administration (FDA)-approved antitumor agents, having been in use in the clinic for well over four decades. Though this chemotherapeutic agent is reasonably effective, it is not very selective. The drug affects many sites and is thus very poorly tolerated. Over the years, there has been much research devoted to devising more site-selective related compounds. It was established that a heterocyclic ring in this compound is opened metabolically and then discarded. The active alkylating metabolite comprises the relatively small molecule commonly known as the "phosphoramide mustard".



Cyclophosphamide | Phosphoramide Mustard | Glutathione