Published in final edited form as:

Asian J Org Chem. 2018 August ; 7(8): 1448–1466. doi:10.1002/ajoc.201800255.

Nature Inspired Molecular Design: Stereoselective Synthesis of Bicyclic and Polycyclic Ethers for Potent HIV-1 Protease Inhibitors

Arun K. Ghosh, Margherita Brindisi^a

^[a]Department of Chemistry and Department of Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907 (USA)

Abstract

We have developed a conceptually new generation of non-peptidic HIV-1 protease inhibitors incorporating novel structural templates inspired by nature. This has resulted in protease inhibitors with exceptional potency and excellent pharmacological and drug-resistance profiles. The design of a stereochemically defined *bis*-tetrahydrofuran (*bis*-THF) scaffold followed by modifications to promote hydrogen bonding interactions with the backbone atoms of HIV-1 protease led to darunavir, the first clinically approved drug for treatment of drug resistant HIV. Subsequent X-ray crystal structure-based design efforts led us to create a range of exceptionally potent inhibitors incorporating other intriguing molecular templates possessing fused ring polycyclic ethers with multiple stereocenters. These structural templates are critical to inhibitors' exceptional potency and drug-like properties. Herein, we will highlight the synthetic strategies that provided access to these complex scaffolds in a stereoselective and optically active form, enabling our medicinal chemistry and drug development efforts.

Graphical Abstract

akghosh@purdue.edu.

This Paper is dedicated to Professor E. J. Corey on the occasion of his 90th birthday

Conflict of interest

The authors declare no conflict of interest.

Keywords

cyclic ethers; drug discovery; HIV-1 protease inhibitors; Natural products; synthesis

1. Introduction

Organic synthesis is an enabling science with immense impact in many areas of science including modern medicine and biology.^[1–3] The field of organic synthesis has markedly expedited drug-discovery and drug development research since the late 20th Century, leading to the development of numerous breakthrough medicines and first-in-class drugs.^[4–6] Over the years, our research interest in the synthesis of bioactive natural products has had two major objectives. The first objective is to develop new reactions in the context of our synthesis.^[7,8] The second and perhaps more important objective is to explore the chemistry and biology of these rare bioactive natural products by elucidating the biological mechanism of action and unraveling medicinal potential.^[9–12] Subsequently, this has provided a unique perspective to our research interests in the area of design and synthesis of intriguing molecular probes or small molecule modulators for biological targets. Our accomplishments in the synthesis of complex natural products, and the development of various asymmetric methodologies also provided considerable expertise, experience and insights into our molecular design and synthesis. This led to development of numerous new and unprecedented structural templates, ligands and scaffolds for drug design and medicinal

chemistry. In the following section, we provide highlights of one aspect of our molecular design and drug development.

The emergence of acquired immunodeficiency syndrome (AIDS) in the early 1980s marked the beginning of a global pandemic.^[13,14] The human immunodeficiency virus type 1 (HIV-1) was subsequently discovered as the causative agent of AIDS.^[15,16] Molecular events critical to virus replication identified several important biochemical targets; including reverse transcriptase, protease, and integrase for antiviral drug development.^[17,18] Among them, HIV-1 protease was specifically attractive due to its key role in processing the gag and gag-pol gene products into essential viral proteins required for assembly of a new mature virus.^[19,20] This led to intense research efforts in the design and synthesis of HIV-1 protease inhibitor drugs for treatment of HIV infection and AIDS in academic and pharmaceutical laboratories.^[21,22] HIV-1 protease inhibitors are now an important component of highly active antiretroviral therapy (ART) for the management of HIV-1 infection and AIDS.^[22,23] Saquinavir (1, Figure 1) is one of the first FDA approved HIV-1 protease inhibitors.^[24,25] The development of protease inhibitors and their combination with reverse transcriptase inhibitors in the late 1990s marked the beginning of an important era of HIV/AIDS management.^[26,27] The use of ART dramatically reduced AIDS-related deaths in HIV/AIDS patients who have access to these therapies.^[28,29] The development of saquinavir further highlights the importance of structure-based design. The X-ray structure of saquinavir-bound HIV-1 protease provided molecular insight into the inhibitor and the HIV-1 protease interactions in the active site.^[30,31] While the discovery of saquinavir is an early important breakthrough, there are severe limitations with saquinavir-like drugs. This drug contains peptide-like features. As a result, higher therapeutic doses are required, which lead to many debilitating side effects. Also, one of the major concerns for saquinavir-based therapies is the emergence of drug resistance, which renders treatment ineffective within a short period of time.^[32,33] We became interested in saquinavir because of its proven clinical efficacy, its X-ray crystallography, and known detailed structure–activity relationship studies.^[24,30] Based upon these results, we set out to devise a conceptually new generation of non-peptidic HIV-1 protease inhibitors with novel scaffolds and templates by drawing our inspiration from nature.^[7,8] The ultimate objective was to create a new class of inhibitors with novel structural features and improved pharmacological and drug-resistance profiles. These research efforts led to the design and discovery of a new class of exceedingly potent inhibitors with unique structural features. One of these inhibitors is darunavir (2, Figure 1), which showed good drug-like properties and maintained superb activity against a wide range of drug-resistant HIV-1 variants.^[34–36] Darunavir was approved by the FDA as the first-line therapy for treatment of patients with HIV infection and AIDS.^[37,38] In darunavir, we have designed and incorporated a stereochemically defined and conformationally constrained template, *bis*-tetrahydrofuran (*bis*-THF) to promote hydrogen bonding interactions with the backbone atoms at S2-sub-site.^[8,39] Subsequently, our X-ray crystal structure-based design efforts led us to create a range of exceptionally potent inhibitors where we incorporated other intriguing ligands such as *3S*-THF, *Cp*-THF, *Tp*-THF, *tris*-THF and *Cm*-THF.^[40–43] These ligands were designed to promote extensive hydrogen bonding interactions with the active site protein backbone atoms of HIV-1 protease. This backbone binding concept has been a fruitful design strategy for combating drug-resistant HIV-1 variants.^[40] In inhibitor **3**

(Figure 1), we have designed a 6-5-5-ring-fused crown-like-tetrahydropyranofuran as the P2-ligand, an aminobenzothiazole as the P2' ligand and a two-fluorine containing Phe-side chain as the P1-ligand.^[44,45] This inhibitor exhibited an unprecedented antiviral activity against a wide range of highly multidrug-resistant HIV-1 variants, displayed a high genetic barrier against the emergence of resistant variants, showed very potent inhibition of dimerization of protease monomers and penetrated the CNS favorably.^[43,44] In our adventure with nature-inspired molecular design, the ligand templates we have created possess fused ring systems as well as stereochemical complexity due to the presence of multiple stereocenters. Herein, we outline our syntheses of these complex scaffolds, which were carried out in stereodefined and optically active form. The outlined synthetic strategies and expedient organic synthesis have been critical to our medicinal chemistry and drug development endeavors.

2. Natural Products Inspired Molecular Design: Cyclic Ethers to Mimic Peptide Bonds

Historically, natural products have been an incredible source for structural diversity and development of new drugs. An estimated 60% of clinically-approved drugs are either natural products or natural product-derived molecules.^[46,47] Optimized over millions of years of evolution in biological micro-environments, organisms have fine-tuned a variety of molecules, molecular scaffolds and templates to interact with their respective biological counterparts.^[48,49] Many structural templates, scaffolds, and functionalities inherent to natural products motivated us to incorporate these features in our molecular design.^[50,51] We have been particularly intrigued with the cyclic ether and cyclic acetal scaffolds present in numerous bioactive natural products. As can be seen in Figure 2, natural products such as monensin (**4**),^[52] azadirachtin (**5**),^[53] ginkgolide (**6**),^[54] and platensimycin (**7**),^[55] contain cyclic ether and cyclic acetal scaffolds and display very potent biological activity. The syntheses of these bioactive targets show exceptional mastery of the art and power of organic synthesis. However, we were particularly intrigued with the cyclic ether templates as these features are very likely involved in specific interactions with peptides or proteins. How do these specific molecular features interact with their respective target protein or receptor? We hypothesize that the cyclic ether oxygens may be positioned to mimic the carbonyl binding of peptide bonds by making polar hydrogen bonding interactions. In fact, an X-ray crystal structure (PDB Code:3HNZ) of platensimycin bound to its target, the Gram-positive bacterial enzyme beta-ketoacyl synthase II (FabF), revealed that the cyclic ether oxygen formed a strong hydrogen bond with the Thr270 residue of the enzyme.^[56] Furthermore, it is also logical to assume that the stereochemically defined substituents and side chains on the cyclic rings may be mimicking the hydrophobic interactions from amino acid side chains of peptides and proteins. During biosynthesis, these molecules were close to their biosynthetic enzymes and also, as they exhibit high affinity to target enzyme or receptor, it is conceivable that cyclic ether templates can be customized in molecular design to mimic the peptide bond. This would provide an incredible opportunity to design novel 'nonpeptide' molecular probes against bioactive peptides or proteins and alleviate problems related to peptide and peptidomimetic drugs. These structural features are stable and time-tested as nature has been optimizing them for millions of years. This has inspired our molecular design of a new

generation of conceptually and structurally novel HIV-1 protease inhibitors for the treatment of HIV infections and AIDS.

3. Design of Conceptually New Cyclic Ether-derived Protease Inhibitors: From Saquinavir to Darunavir

Saquinavir (Ro 31–8959) is one of first HIV-1 protease inhibitor drugs approved for treatment of HIV/AIDS.^[57,58] A number of other first-generation inhibitors were developed and approved later on, namely ritonavir,^[59] indinavir,^[60] nelfinavir^[61] and amprenavir.^[62] However, the therapeutic efficacy of these first-generation drugs was limited due to high metabolic instability, low half-life, poor oral bioavailability and other significant side effects. The majority of these protease inhibitor drugs are peptidic in nature and these problems are related to peptide-based drugs. The emergence of drug-resistant strains of HIV represented a major problem for these first-generation protease inhibitors. Research efforts aimed at addressing these issues led to the development of second-generation inhibitors, such as lopinavir,^[63] atazanavir^[64] and tipranavir^[65] with improved overall drug-like profiles. However, the emergence of resistant HIV-1 variants from experienced patients still represented a relevant hurdle.

A high-resolution X-ray crystal structure of Saquinavir-bound HIV-1 protease revealed a number of key ligand-binding site interactions.^[31,66] It turned out that the P2-asparagine side chain carbonyl oxygen and the P3-quinaldic amide carbonyl oxygen formed hydrogen bonds with the backbone NHs of Asp30 and Asp29 in the S2- and S3-subsites, respectively.

In our early efforts to reduce peptidic features in HIV-1 protease inhibitors, such as saquinavir, we explored stereochemically defined tetrahydrofuran derivatives and sulfolane derivatives to replace amide bonds and mimic the biological mode of action with heterocyclic templates. This effort led to the design and synthesis of a variety of potent HIV-1 protease inhibitors. Subsequently, based upon detailed X-ray structural studies of saquinavir and other inhibitor-bound HIV-1 protease complexes, we designed a fused bicyclic tetrahydrofuran that could effectively form hydrogen bonds with Asp29 and Asp30 backbone NHs similar to the asparagine carbonyl and quinaldic amide carbonyl of saquinavir. These efforts led to the design of inhibitors **8** and **9** (Figure 3), in which we intended to replace both P2 and P3-amide groups of saquinavir with a *bis*-THF ligand. Furthermore, we speculated that the binding affinity of the conformationally constrained *bis*-THF may offset the loss of hydrophobic interaction due to the P3-quinoline ring of saquinavir. Indeed, inhibitor **8** containing a stereochemically defined (*3R*, *3aS*, *6aR*)-*bis*-tetrahydrofuranyl urethane showed very potent enzyme inhibitory and antiviral activity. Our detailed structure–activity relationship studies revealed that ring stereochemistry, positions of oxygens, ring size, and substituents are all critical to optimize binding interactions.

Following the discovery of the cyclic-ether-derived *bis*-THF ligand, in an effort to enhance the interactions with the active site of HIV-1 protease, we incorporated both enantiomers of the *bis*-THF ligand in the (*R*)-(hydroxyethyl)sulfonamide isostere with a *p*-methoxybenzene sulfonamide as the P2' ligand.^[67] Since HIV-1 protease is a homodimer, based upon the X-ray structure of inhibitor **8**-bound HIV1 protease, we particularly planned to design

inhibitors that would maximize hydrogen bonding interactions with both halves of the HIV-1 protease active site, particularly with the backbone atoms. We formulated this design strategy on the basis of the observation that the backbone conformation of the active sites of various mutant proteases is only minimally distorted compared to wild-type HIV-1 protease. [22]

We speculated that such inhibitors will likely maintain those active site interactions with other protease mutants and essentially, slow down emergence of drug-resistant HIV-1 variants due to possible reduction of catalytic fitness. We incorporated both *bis*-THF enantiomers with a (*R*)-hydroxyethyl *p*-methoxy benzenesulfonamide isostere which provided inhibitors **10** and **11** (Figure 4).

Inhibitor **10** (later named TMC-126) exhibited remarkable HIV-1 inhibitory potency and antiviral activity. Inhibitor **11** with the enantiomeric *bis*-THF was less potent in our antiviral assay.^[68] A preliminary X-ray structure of **10**-bound HIV-1 protease evidenced our expected network of backbone hydrogen bonding interactions at both the S2 and S2' subsites.

Our in-depth drug-sensitivity studies showed that viral acquisition of resistance to **10** was substantially delayed and the inhibitor was highly potent against a panel of highly multi-PI-resistant HIV-1 strains.^[69,70]

Further optimization of the P2'-sulfonamide functionalities with the goal of promoting hydrogen bonding interactions with the backbone atoms at the S2' subsite led to the identification of a number of very potent inhibitors. Particularly, inhibitor **2** (later named TMC-114) bearing a *bis*-THF as the P2 ligand and a *p*-aminobenzenesulfonamide as the P2' ligand displayed unprecedented broad-spectrum antiviral activity against a wide range of multidrug-resistant HIV-1 variants. These results were very encouraging since these viral strains were isolated from patients with HIV/AIDS who had failed to respond to 9 to 11 other anti-HIV drugs. Subsequently, we have also shown that inhibitor **2** blocks HIV-1 protease dimerization. This aspect was assessed by means of an intermolecular fluorescence resonance energy transfer (FRET)-based HIV expression assay.^[71] Darunavir received an accelerated approval by the FDA on June 23, 2006, for patients harboring drug-resistant HIV. On October 22, 2008, Darunavir received FDA approval for the treatment of all patients with HIV infection and AIDS.^[72]

We carried out high resolution X-ray crystal structure of the darunavir-HIV-1 protease complex. These structural studies provided critical molecular insight into the ligand-binding site interactions responsible for darunavir's unprecedented antiviral activity and drug-resistance profiles.

Both oxygen atoms of the *bis*-THF form very strong hydrogen bonds with the Asp29 and Asp30 backbone amide NHs in the S2 subsite and the P2'-aminosulfonamide's amine functionality formed hydrogen bonds with the Asp30' backbone NH in the S2'-subsite. Furthermore, the bicyclic ring of the *bis*-THF ligand is involved in van der Waals interactions with residues in the S2 subsite.^[34–36] To further optimize darunavir, we have designed a variety of structural templates that would enhance the backbone-binding interactions, as well as further improve van der Waals interactions in the HIV-1 protease

active site. A number of representative inhibitors and their potency are summarized in Figure 5. These inhibitors are exceptionally potent against a wide range of multidrug-resistant HIV-1 variants. Of particular note, these inhibitors show unprecedented natural product-derived structural features containing multiple stereocenters. While these inhibitors are exceptionally potent, the synthesis of these molecules in quantities necessary for structure–activity relationship studies and also for drug development posed a considerable challenge. Unlike total synthesis endeavors, where the final target molecules are synthesized in milligram quantities, a much larger amount is typically necessary for drug discovery and development work. Synthetic strategies and selection of reactions are required to be practical and reliable for in-depth studies and pre-clinical development. Most importantly, the power of organic synthesis is enabling these new ventures in drug development today. In the following section, we will outline our efforts in organic synthesis to create these inhibitors for possible drug development.

4. Synthesis of darunavir

For the synthesis of darunavir (**2**) we planned to carry out an alkoxycarbonylation^[73] of isostere amine **18** and the activated mixed carbonate of 3-hydroxy-*bis*-tetrahydrofuran (–)-**17** (Scheme 1).^[74] Accordingly, darunavir (**2**) was assembled as shown in Scheme 2. (3*R*, 3*aS*, 6*aR*)-3-Hydroxyhexahydrofuro-[2,3-*b*]furan (*bis*-THF) (–)-**17** was converted to its corresponding activated mixed carbonate **21** by treatment with *N,N*-disuccinimidyl carbonate (**19**, DSC) in the presence of triethylamine.^[74] Hydroxyethylsulfonamide isostere **18** was obtained from epoxide **20** by a four-step process, involving (a) epoxide opening by treatment with isobutylamine, (b) reaction with *p*-nitrobenzenesulfonyl chloride, (c) catalytic hydrogenation of the nitro group, and (d) Boc deprotection. Final alkoxycarbonylation of the primary amine **18** with activated *bis*-THF **21** provided darunavir (**2**) in 85% yield for the three steps.^[74,75]

4.1 Chemistry of the *bis*-THF ligand

As soon as we recognized the importance of the *bis*-THF moiety in the design of potent PIs, it became necessary to devise a suitable and convenient route for its synthesis. We herein outline various syntheses of *bis*-THF ligand developed by us over the years. Our initial synthesis of optically active *bis*-THF utilized diethyl malate as the key starting material (Scheme 3).^[76] As shown, Seebach alkylation on compound **22** represented the key step of the synthesis. Alkylation of **22** with allylbromide proceeded in a highly stereoselective manner providing alkylation product with 12:1 diastereomeric ratio and 85% yield. Reduction of the ester functionalities of **23** followed by acetonide protection provided alcohol **24**. Oxidation of this latter to the corresponding aldehyde and subsequent acid-catalyzed cyclization furnished the corresponding lactol **25** in 4:1 diastereomeric ratio. Ozonolysis followed by acid-catalyzed cyclization resulted in the desired *bis*-THF ligand (–)-**17** in optically pure form.^[76] Although this synthetic route provided the stereochemical identity of the *bis*-THF ligands, it proved to be ineffective for either large-scale preparation or the synthesis of structural variants. Later on, we developed a very convenient three-step synthesis of racemic *bis*-THF followed by immobilized lipase-catalyzed enzymatic resolution to provide ample quantities of (3*R*, 3*aS*, 6*aR*)-3-hydroxyhexahydrofuro[2,3-

b]furan (–)-**17** in high enantiomeric excess (>96% *ee*) (Scheme 4).^[77] Commercially available 2,3-dihydrofuran **26** was reacted with *N*-iodosuccinimide and propargyl alcohol to provide the corresponding racemic alkyne **27**. Radical cyclization using cobaloxime (**28**) and sodium borohydride afforded the desired *bis*-THF precursor **29**. Ozonolysis followed by reductive workup provided the racemic *bis*-THF ligand (±)-**17**. Following lipase resolution resulted in the desired chiral ligand (–)-**17** and acetate (+)-**30**. Optical purity of (–)-**17** was determined as >95% *ee* by Mosher ester analysis.^[77]

We also reported a photochemical route involving a stereoselective photochemical 1,3-dioxolane addition to 5(S)-benzyloxymethyl-2-(5*H*)-furanone **31** as the key step (Scheme 5).^[74] Irradiation of **31** in the presence of benzophenone led to dioxolane **32** as a 96:4 mixture of *anti/syn* isomers. Catalytic hydrogenation of **32** provided alcohol **33**. Reduction with lithium aluminum hydride and acid-catalyzed cyclization furnished *bis*-THF derivative **34** in good yields. Epimeric alcohol **34** was then converted into the desired *bis*-THF derivative (–)-**17** via Mitsunobu inversion. The same compound could also be prepared by a two-step oxidation/reduction sequence via TPAP/NMO oxidation of **34** to the corresponding ketone, which is then reduced with sodium borohydride to afford optically active *bis*-THF (–)-**17** as a single isomer.

In 1999 we developed a multi-component reaction which involved the addition of ethyl glyoxalate **35** to 2,3-dihydrofuran **26** mediated by titanium tetrachloride to give tetrahydrofuranyl-derivative **36**.^[78] This method was utilized for the synthesis of large amounts of the racemic *bis*-THF alcohol **17** (Scheme 6).^[79] Compound **36** was reduced to the corresponding diol **37** and cyclized to provide racemic alcohol **17**. A three-step process including a TEMPO oxidation, a sodium borohydride reduction and a lipase resolution as described above finally provided the optically active *bis*-THF ligand (–)-**17**.

Another synthesis of optically active *bis*-THF utilized an ester-derived *anti*-aldol reaction developed in our laboratories (Scheme 7).^[80] Treatment of the titanium enolate of **38** with a precomplexed cinnamaldehyde and TiCl₄ led to the *anti*-aldol product **39**. The aldol product was reduced by lithium aluminum hydride to provide alcohol **40**. Swern oxidation and protection of the resulting aldehyde as dimethoxyacetal furnished product **41**. It was converted to the optically pure *bis*-THF (–)-**17**.

Our recent route for *bis*-THF synthesis started from known optically active alcohol **43**, that was *O*-alkylated with *tert*-butyl bromoacetate **42** (Scheme 8).^[81] The resulting ether **44** was subjected to an efficient [2,3]-sigmatropic rearrangement to furnish compound **45**. Reduction of its corresponding mesylate provided alcohol **46**. Oxidative cleavage of the terminal alkene followed by acid-catalyzed cyclization afforded the desired *bis*-THF alcohol (–)-**17**.

4.2 Synthesis of the Epoxide Subunit

As shown in Scheme 2, darunavir (**2**) was synthesized in a convergent manner using the *bis*-THF alcohol (–)-**17** and an isosteric amine derivative **18** which was synthesized from optically active aminoalkyl epoxide **20**. We developed a number of efficient syntheses for these isosteric amines for optimization of drug potency and drug properties. Scheme 9

outlines an asymmetric synthesis of epoxide **20** employing a Sharpless epoxidation as the key step.^[82] The synthesis started from phenylmagnesium bromide which was treated with commercially available 1-butadiene monoxide (**47**) in the presence of catalytic CuCN providing the allylic alcohol **48**. Subsequent Sharpless epoxidation of **48** afforded the corresponding optically active epoxide **49** which was subjected to an epoxide ring opening reaction affording azidoalcohol **50**. Treatment with 2-acetoxybutyryl chloride provided desired azidoepoxide **51**. Catalytic hydrogenation of **51** in the presence of di *tert*-butyl dicarbonate afforded epoxide **20**.

Another convenient synthesis of epoxide **20** was developed starting from commercially available Boc-protected phenylalanine. As shown in Scheme 10, protected phenylalanine **52** was converted to alcohol **53** in a three-step sequence, involving reaction of **52** with isobutyl chloroformate followed by treatment with diazomethane to give the corresponding diazoketone. Subsequent reaction with HCl provided the corresponding chloroketone, finally reduced with NaBH₄ to provide **53** in good yield. Treatment of **53** with alcoholic KOH quantitatively afforded epoxide **20**.^[83]

5. Cp-THF containing inhibitors

We developed a variety of exceptionally potent HIV-1 protease inhibitors through the design of a stereochemically defined bicyclic hexahydrocyclopenta[*b*]furan moiety (*Cp*-THF) as the P2 ligand (Figure 6). The combination of *Cp*-THF as the P2 ligand and a *p*-hydroxymethylphenylsulfonamide as the P2' ligand resulted in inhibitor **12**, which exhibited exceptional potency.^[41] Compound **54**, containing a *p*-aminobenzenesulfonamide as the P2' ligand also showed very potent inhibitory properties.

5.1 Synthesis of *Cp*-THF ligand.

The potency enhancing effect of the *Cp*-THF ligand is possibly due to its strong backbone hydrogen bonding interactions as well as van der Waals interactions in the S2 subsite. We developed an efficient synthetic route to (*3aS*, *5R*, *6aR*)-5-hydroxyhexahydrocyclopenta[*b*]furan (*Cp*-THF, **58**) in optically active form (Scheme 11).^[41] This initial synthesis was based upon an enzymatic asymmetrization providing a monoacetate derivative in multigram scale.^[84] After protection of its free hydroxyl group as silyl ether (**55**), hydrolysis followed by treatment with ethyl vinyl ether and *N*-bromosuccinimide furnished the bromo acetal **56**. Radical cyclization provided bicyclic acetal **57**. Its subsequent reduction followed by deprotection afforded optically active alcohol **58** (*Cp*-THF).

With the goal to broaden the scope and utility of the *Cp*-THF-derived inhibitors, we also carried out a convenient enantioselective synthesis of the *Cp*-THF ligand utilizing commercially available (1*R*,5*S*)-(+)-2-oxabicyclo[3.3.0]oct-6-en-3-one (**59**) (Scheme 12).^[85] This route gave access to quantities of the *Cp*-THF ligand **58** in high optical purity. Stereoselective installation of the C5-hydroxyl group was accomplished by an oxymercuration-demercuration protocol in a *one-pot* fashion. Treatment with aqueous sodium hydroxide followed by sodium borohydride furnished the *endo*-alcohol **60** as a

single diastereomer. Protection of the hydroxyl group as a silylether and reduction of the resulting silyloxylactone led to diol **61** in excellent yield. Subsequently, selective mesylation of the primary alcohol followed by reaction with sodium hydride and final deprotection led to optically active *Cp*-THF (**58**).

The above-mentioned procedure was less suitable for a scale-up of the *Cp*-THF ligand as it involved the use of large amounts of mercuric acetate and a tedious work up with mercury byproducts. We later finalized a practical bromohydrin route (Scheme 13).^[85] Reaction of **59** with *N*-bromosuccinimide provided bromohydrin **62**. Alternative bromohydrin **63** was also formed as a significant byproduct. Two alternatives for the reduction of bromohydrin **62** were investigated, namely i) the use of tri-*n*-butylstannane in the presence of AIBN and ii) a catalytic hydrogenation employing catalytic amounts of pyridine. The resulting lactone **60** was submitted to a two-step reduction; reaction with DIBAL-H provided the corresponding lactol, in turn treated with triethylsilane in the presence of titanium tetrachloride to afford the desired optically active *Cp*-THF **58**.

To circumvent the formation of isomeric lactone **63**, we further investigated the bromohydrin reaction with the corresponding 3-derived tetrahydro-2*H*-cyclopenta[*b*]furan derivative (**59**) (Scheme 14).^[85] The above-mentioned two-step reduction with DIBAL-H and triethylsilane provided **64**. Following reaction with NBS provided a mixture of diastereomeric bromohydrins **65** and **66** (3.5 to 1, respectively). Reduction of bromohydrin **65** afforded optically active *Cp*-THF **58**. The minor isomer **66** was also converted to alcohol **58** by debromination of the epimeric alcohol and then by an oxidation/reduction sequence using TPAP and sodium borohydride.

6. Development of high affinity P2 ligands

6.1 Tris-THF containing inhibitors

The X-ray structure of darunavir-bound HIV-1 protease provided further molecular insight to enhance ligand-binding site interactions. We speculated that the incorporation of an additional tetrahydrofuran ring on the *bis*-THF ligand would provide further possibility for interaction at the S2 level. The envisaged oxatricyclic moiety could display a variety of stereochemical possibilities, including a *syn-syn-syn* (*SSS*-type) and a *syn-anti-syn* (*SAS*-type) configuration. Both the tricyclic scaffolds were synthesized and the corresponding inhibitors **67** (*SSS*-type) and **68** (*SAS*-type) were tested (Figure 7).^[42] Inhibitor **67** showed good inhibitory activity however, compound **68** exceeded its potency by about 10-fold. Both compounds showed excellent antiviral activities.^[86] Additionally, compound **68** blocked HIV-1 protease dimerization about 10-fold better than darunavir. The additional THF ring of **68** was involved in water-mediated hydrogen bonds with Asp29, Gly27 and Arg8' (at the dimer interface). Furthermore, the *tris*-THF ring could adequately fill the hydrophobic pocket in the S2 subsite neatly packing against the P1-phenyl group of the inhibitor, thus allowing improved hydrophobic contacts.^[42]

The synthesis of the *SSS*-type oxatricyclic *tris*-THF ligand is shown in Scheme 15.^[42] Optically active *bis*-THF alcohol (–)-**17** was converted into the corresponding bicyclic enol-ether via the iodide. The following reaction with *N*-iodosuccinimide and propargyl alcohol

afforded iodoether **69**. Radical cyclization provided tricyclic olefin, subsequently submitted to ozonolytic cleavage providing ketone **70**. Extensive NMR experiments were performed to correctly establish the stereochemistry of the tricyclic core. Finally, *L*-selectride reduction provided alcohol **71** as a single isomer.

The synthesis of the *SAS*-type oxatricyclic *Tris*-THF ligand is shown in Scheme 16.^[42] After saponification, acetate (+)-**30** was converted to the bicyclic enol-ether **72** as described above. Conversion of this into the corresponding epoxide was followed by epoxide opening with catalytic sodium methoxide. Dess–Martin oxidation and subsequent *L*-selectride reduction of the resulting ketone provided the desired *endo*-alcohol **73**. Acylation of **73** and subsequent treatment with propargyl alcohol afforded acetals **74** and **75** in 1:4 ratio. Removal of the acetate provided the corresponding mixture of alcohols. The major diastereomeric alcohol deriving from **75** was converted into the corresponding tricyclic olefin **76**. This was submitted to ozonolytic cleavage followed by reduction to provide *SAS*-type oxatricyclic *Tris*-THF **77** as a single isomer.

6.2 Dioxatriquinane-derived P2-ligands

In an effort to examine the contribution of the middle oxygen of the *tris*-THF ligand toward the ligand binding site interactions, we sought to synthesize the corresponding *SAS*- and *SSS*-fused 1,6-dioxatriquinane derivatives **78** and **79** (Figure 8).^[87] Both compounds are very potent, however the inhibitory activity is significantly lower than the *SAS*-fused *tris*-THF-derived inhibitor **68**, thus demonstrating that the hydrogen bonding ability of the second oxygen in the *tris*-THF is critical to potency.

For the synthesis of *SSS*- and *SAS*-fused alcohols **85** and **87** we employed a cascade radical cyclization (Scheme 17).^[87] For *SSS*-fused ligand **85**, the hydroxyl group of monoacetate **80** was protected as the TBS-ether with TBSCl in the presence of imidazole. Hydrolysis of the resulting acetate afforded alcohol **81**. Treatment of alcohol **81** with NBS and ethyl vinyl ether provided bromo acetal **82** as a mixture (1:1) of diastereomers. Removal of the TBS group with TBAF provided the corresponding alcohol, subsequently treated with NaH and propargyl bromide affording the radical cyclization precursor **83**. The cascade cyclization using tri-*n*-butyltin hydride in refluxing toluene in the presence of AIBN, followed by reduction of the resulting acetal with Et₃SiH in the presence of BF₃·OEt₂ afforded tricyclic alkene **84** as a single isomer. Ozonolytic cleavage followed by reduction of the resulting ketone with NaBH₄ provided the desired ligand **85** in good yield. *SAS*-fused ligand **87** was obtained following a similar pathway after Mitsunobu inversion of alcohol **81**.

6.3 C4-substituted *bis*-THF ligands

In an effort to further modulate ligand-binding site interactions of the *bis*-THF ligand, we subsequently explored substitution at the C4 position of the *bis*-THF ligand. We showed that incorporation of a methoxy substituent at C4 promoted the formation of a key water-mediated hydrogen bond with the amide NH of Gly-48 located at the flap of the HIV-1 protease.^[81] We then sought to introduce *gem*-difluorines at the C4 position. This resulted in inhibitor **88** (Figure 9) which exhibited strong non-bonded interactions with the carbonyl group of Gly48 through the *gem*-difluorines in the flap region of HIV-1 protease.^[88,89]

These interactions appeared to be responsible for improved inhibitor affinity and antiviral activity against multidrug-resistant HIV-1 variants. The increased lipophilicity due to the presence of two fluorines led to an improvement of the inhibitor's ability to cross the blood-brain-barrier.^[90]

We also speculated that introduction of a secondary amine functionality at the C4 position could lead to strong hydrogen bonding interactions with the Gly48 backbone atoms. Also, the alkyl side chain may effectively fill the hydrophobic pocket in the S2 subsite. Overall, this improvement in backbone interactions and van der Waals interactions may not only result in improvement of antiviral activity against multidrug-resistant HIV-1 variants, but the basic amine may also improve the inhibitor's pharmacological properties.^[91,92] Indeed, compound **15** (Figure 9) with a C4-isopropylamine functionality showed marked antiviral activity with a 10-fold improvement over darunavir.^[91]

The synthesis of stereochemically defined *gem*-difluoro derivatives of *bis*-THF **97** is shown in Schemes 18 and 19.^[89] DIBAL-H reduction of ester **89** provided dibenzyl-*L*-glyceraldehyde. Horner–Emmons reaction of the resulting aldehyde provided α,β -unsaturated ester **90** in excellent yield. Reduction of **90** with DIBAL-H provided the corresponding allylic alcohol^[93] which was treated with chlorodifluoroacetic acid to afford difluoro acetate derivative **91**. The latter was then exposed to Reformatsky–Claisen reaction^[94] by treatment with TMSCl and activated Zn-dust. Subsequent esterification of the crude acid product with a catalytic amount of concentrated H₂SO₄ in ethanol provided a 2:1 mixture of diastereomers **92**. The mixture was converted to the corresponding Weinreb amides separable by silica gel chromatography to provide *syn*-diastereomer **93** as the major product and *anti*-diastereomer **94** as the minor product in a 2:1 ratio (Scheme 18). The assignment of stereochemistry was carried out based upon reported ¹H-NMR data for the corresponding diastereomer.^[93]

The synthesis of *gem*-difluoro derivative **97** is shown in Scheme 19.^[89] Reduction of Weinreb amide **93** with LAH followed by aldehyde reduction with NaBH₄ provided difluoro alcohol **95** in near quantitative yield. Ozonolysis of the olefin followed by reductive cleavage with triphenylphosphine provided crude cyclic acetal **96**, upon cyclization. The resulting cyclic acetal was then subjected to catalytic hydrogenation over Pearlman's catalyst to furnish the corresponding triol. Treatment of the resulting triol with a catalytic amount of CSA afforded optically active difluoro-*bis*-THF **97** in 68% yield over 3 steps.

Synthesis of the optically active Boc-protected C-4 isopropylamino *bis*-THF derivative **105** is shown in Scheme 20.^[91] The α,β -unsaturated isopropylidene derivative **98** was synthesized from commercially available *D*-mannitol as reported.^[81] DIBAL-H reduction of **98** provided an allylic alcohol which was reacted with *tert*-butyl bromoacetate in the presence of cesium hydroxide to afford *O*-alkylation product **99**.^[95] Reaction of **99** with LiHMDS provided the sigmatropic rearrangement product α -hydroxy ester **100** as the major product.^[96] The α -hydroxy ester **100** was converted into the corresponding benzyl ether **101** and then to *bis*-THF derivative **102** in a three-step sequence involving, i) reduction of **101** by LAH, ii) ozonolytic cleavage of the olefin to form an aldehyde, and iii) reaction of the resulting crude aldehyde with *p*-TsOH to provide *bis*-THF alcohol **102**. Alcohol **102** was

converted to azide **103** under Mitsunobu conditions.^[97] Azide **103** was reduced to the corresponding amine under hydrogenation conditions. The amine underwent reductive amination in the presence of acetone and sodium borohydride to afford the isopropylamine derivative **104**. Boc protection of the resulting amine with Boc anhydride and catalytic hydrogenation over Pearlman's catalyst finally provided the Boc-protected isopropylamino *bis*-THF derivative **105** to be employed in inhibitor synthesis.

6.4 Tp-THF containing inhibitors.

In an effort to further optimize the *bis*-THF structural template of darunavir, we explored modifications that would enhance the "backbone binding" as well as improve hydrophobic interactions in the protease active site. Toward this aim, new highly potent HIV-1 protease inhibitors, incorporating a variety of more flexible cyclic ethers/polyethers as the P2-ligand, were designed and synthesized within our research group over the years.^[92,98–100]

In particular, we planned to investigate the advantages of a ring size increase in the bicyclic structure of *bis*-THF. Particularly, stereochemically defined (*3aS,4S,7aR*)-hexahydro-2*H*-furo[2,3-*b*]pyran-4-ol (*Tp*-THF) was conceived as novel P2 ligand. This was to achieve a closer interaction with the Asp30 with respect to the *bis*-THF ligand, simultaneously promoting, with the additional methylene, more favorable van der Waals interactions within the hydrophobic pocket in the S2 subsite. Furthermore, the larger ring size would enhance flexibility creating to an improved adaptability to protease mutations. The resulting compound **13** (Figure 10) showed very potent enzyme inhibitory and antiviral activity. Furthermore, inhibitor **13** is highly potent against a panel of multidrug-resistant HIV-1 variants. The X-ray structural analysis revealed that the hydrogen bonding interactions of both P2 ligand oxygens are significantly stronger than those established by the *bis*-THF ligand in darunavir.^[101]

Our initial synthetic approach to optically active (*3aS,4S,7aR*)-hexahydro-2*H*-furo[2,3-*b*]pyran-4-ol **109** is shown in Scheme 21.^[101] Lactone **106**^[102] was reduced into the corresponding diol using lithium aluminum hydride. Selective monoacetylation at the primary alcohol using AcCl^[103] followed by silylation of the remaining free hydroxyl functionality afforded intermediate **107** in excellent yield. Removal of the acetate group, followed by ozonolysis of the olefin, furnished a bicyclic *bis*-acetal intermediate. Reduction of the hemiacetal moiety employing Et₃SiH and BF₃·Et₂O afforded bicyclic intermediate **108**. Removal of the silyl group provided the desired *Tp*-THF ligand **109**.

To expand the use of the *Tp*-THF ligand, we have further explored an alternative synthetic route using readily available and inexpensive starting materials by employing an efficient enzymatic desymmetrization of a *meso*-diacetate as the key step.^[104] The synthesis is shown in Scheme 22. *cis-meso*-Diacetate **110** was prepared in multigram quantity from commercially available, inexpensive, 1,2,3,6-tetrahydrophthalic anhydride by LAH reduction followed by acetylation as reported in the literature.^[104,105] Enzymatic desymmetrization of *meso*-diacetate **110** by treatment with Porcine Pancreatic Lipase (PPL, 5% w/w, Sigma, type II, crude) in 0.1M phosphate buffer (pH 7) over 24 h afforded optically active monoacetate **111** in >95% ee. During this enzymatic reaction, aqueous 1 N NaHCO₃

was added dropwise to neutralize the acetic acid formed during the reaction. Monoacetate **111** was oxidized using a Swern oxidation protocol, providing the corresponding aldehyde in 94% yield. Protection of the aldehyde with trimethyl orthoformate and a catalytic amount of CSA (0.2 equivalent) in the presence of anhydrous MgSO₄ provided acetal **112** in high yield. Oxidative cleavage of the olefin by ozonolysis followed by reduction of the resulting crude dialdehyde with sodium borohydride afforded diol **113**. Treatment of diol **113** with a catalytic amount (30 mol%) of CSA led to bicyclic acetal **114**. Cleavage of the acetate group was carried out by treatment of **114** with potassium carbonate in methanol. The resulting alcohol underwent an elimination reaction using a protocol developed by Grieco and co-workers.^[106] Accordingly, treatment with *o*-nitrophenyl-selenonitrile and *n*-tributylphosphine provided the corresponding selenide derivative. Oxidation of the resulting selenide with *m*-CPBA resulted in the elimination of the corresponding selenoxide to afford olefin **115** in good yields. We carried out oxidative cleavage of exocyclic olefin **115** by ozonolysis. Reduction of the resulting ketone with sodium borohydride in ethanol provided desired *Tp*-THF alcohol **109** in excellent yield.

6.5 Development of Crn-THF-based inhibitors

To promote stronger hydrogen bonds with the top oxygen of *bis*-THF and *Tp*-THF, we further envisaged a larger seven-membered ring for increasing the dihedral angle of the bicyclic acetal template and thereby positioning the top oxygen closer to the Asp30 backbone amide NH. Since the conformation of a seven-membered ring is usually labile, we sought to incorporate a bridged methylene group on the seven-membered ring to limit conformational flexibility and increase stability. This led to newly designed ligands incorporating three extra methylene groups over *bis*-THF and two-extra methylenes with respect to *Tp*-THF. The additional methylene groups could play a pivotal role in favoring van der Waals interactions in the S2-subsite. A larger ring as the P2 ligand with some degree of flexibility could also guarantee better adaptability to protease mutation.

Accordingly, we designed a crown-like-tetrahydropyranofuran (*Crn*-THF) derivative as the novel P2-ligand.^[45] Furthermore, we speculated that with new interactions in the S2-subsite, it may be necessary to optimize the P2'-sulfonamide ligand as well. To promote further hydrogen bonding interactions as well as to improve hydrophobic contacts in the S2'-subsite, we incorporated our *Crn*-THF P2-ligand into an isostere containing a benzothiazole moiety with a small alkylamine. Finally, to increase interactions in the S1-subsite while improving cell and brain penetration, we selected a two-fluorine containing Pheside chain as the P1-ligand. The resulting inhibitor GRL-14213 (**3**) (Figure 11) exhibited exceptional HIV-1 inhibitory and antiviral potency in the picomolar range against a wide panel of highly multidrug-resistant HIV-1 variants.^[43–45] The inhibitor also showed an extremely high genetic barrier against the emergence of drug-resistant variants, potent dimerization inhibitory activity and optimum CNS penetration.^[43,44]

Our synthesis of the *Crn*-THF P2 ligand **122** is shown in Scheme 23.^[36] For the enantioselective synthesis of this unprecedented ligand, we employed a chiral oxazaborolidinium cation catalyzed Diels–Alder reaction developed by Corey and Mukherjee.^[107,108] The appropriate oxazaborolidinium cation **118** was generated in situ

from the corresponding oxazaborolidine (25 mol%) and triflimide (20 mol%) as reported.^[107] The Diels–Alder reaction of readily available ethyl vinyl boronate **116** and cyclopentadiene **117** provided the corresponding cycloadduct which was oxidized with H₂O₂ in the presence of KHCO₃ to afford alcohol **119** in excellent yield on a gram scale. Optical purity of alcohol **119** was determined to be 98% ee by chiral HPLC analysis. Alcohol **119** was protected as TBS ether, and then converted to bicyclic acetal **120** in a three-step sequence involving (i) reduction of the ester with LAH, (ii) one-pot oxidative cleavage of the olefin according to Nicolaou's protocol,^[109] and (iii) reduction of the resulting aldehyde with DIBAL-H to finally provide bicyclic acetal **120** (2:1 mixture). The lactol mixture was treated with TFA to afford the bridged tricyclic derivative, subsequently removing the TBS group to afford alcohol **121** in good yield. This exo-alcohol was converted to its endo-alcohol counterpart **122** by Dess–Martin oxidation followed by reduction of the resulting ketone with NaBH₄ in MeOH. The desired bridged tricyclic ligand, (3*S*,3*aS*,5*R*,7*aS*,8*S*)-hexahydro-4*H*-3,5-methanofuro[2,3-*b*]-pyran-8-ol (**122**) was obtained in 76% yield over two steps. This overall route is quite efficient and provided convenient access to both endo and exo-ligand alcohols in optically active form (>99% ee).

6.6 Synthesis of fluoroepoxides and fluorine-containing isosteres

For the synthesis of fluorinated isosteric amines for GRL-14213 (**3**) and related derivatives, we developed convenient syntheses for fluorine-containing epoxides. Fluorine-containing compounds display increasing importance due to fluorine's ability to improve drug-like features, particularly in terms of BBB and cell penetration.^[43,44,88] Also, fluorine atoms could allow specific interactions with biological targets. Our synthesis of 3,5-difluorobenzene epoxide isostere **126** in optically active form is shown in Scheme 24. Commercially available 1-bromo-3,5-difluorobenzene **123** was converted to its corresponding Grignard reagent. Resulting reaction of 3,5-difluorophenylmagnesium bromide with butadiene monoxide (**47**) in the presence of catalytic CuCN provided allylic alcohol **124** in excellent yield.^[82] This was subjected to Sharpless asymmetric epoxidation^[110,111] using (–)-diethyl-*D*-tartrate to smoothly provide the corresponding epoxide. Regioselective epoxide opening with TMSN₃ and Ti(OiPr)₄ afforded azido diol **125** in good yields.^[112] Reaction of this diol with 2-acetoxyisobutyl chloride afforded the chloroacetate derivative, which was treated with NaOMe to afford desired azidooxirane **126**.^[113]

Recently we reported a highly stereoselective synthesis of Boc-amino difluoroepoxide **130** involving a *syn*-aldol reaction and a Curtius rearrangement as the key steps (Scheme 25).^[114] Accordingly, saponification of *syn*-aldol product **127** with aqueous lithium hydroperoxide was followed by Curtius rearrangement with DPPA in the presence of Et₃N in dry benzene to afford oxazolidinone derivative **128**. This was converted to the Boc-derivative **129** in a two-step sequence involving hydrolysis of **128** with aqueous KOH followed by treatment with *di-tert*-butyl dicarbonate and catalytic hydrogenation. Diol **129** was converted to epoxide **130** by regioselective monotosylation and subsequent exposure of the resulting tosylate to potassium carbonate in methanol. The overall route was also applied to an *anti*-aldol substrate to achieve the diastereoisomeric epoxide.^[114]

Conversion of azidooxirane **126** to the corresponding fluoroisosteric amine **134** and synthesis of inhibitor GRL-14213 (**3**) are shown in Scheme 26. Reaction of azidooxirane **126** with isobutylamine afforded aminoalcohol **131** which was then treated with sulfonyl chloride **132** in the presence of Et₃N to furnish the corresponding sulfonamide derivative.^[44] The azide was subjected to a Staudinger reduction with Ph₃P in aqueous THF. The resulting amine was protected as Boc to provide **133** in very good yield. The methyl sulfide moiety was oxidized to its sulfone derivative with *m*-CPBA. Following treatment with cyclopropylamine, and removal of the Boc group afforded desired difluoroisostere **134** in excellent yield.^[44] Treatment of amine **134** with the activated carbonate of *Cm*-THF ligand (**135**) in the presence of *N,N*-diisopropylethylamine led to GRL-14213 (**3**) in near quantitative yield.

7. Conclusion

The design of molecules that mimic peptide-binding or peptide bonds is fundamentally important in drug discovery and development. Our deep interest in the biology of natural products with polyether structural features led us to design novel structural classes of non-peptide molecules with exceptional potency and favorable pharmacological properties. We have provided highlight of our work on the design and synthesis of a new generation of HIV-1 protease inhibitors. In these inhibitors, we incorporated a variety of natural product-derived templates and scaffolds to mimic peptide bonds. We have been particularly intrigued by the polyether structural features in many bioactive natural products and their possible interactions with their respective biosynthetic enzyme or molecular target for bioactivity. The molecular insights from nature motivated our molecular design. In doing so, our designed inhibitor structures presented significant challenges in synthesis due to structural and stereochemical complexities. The role of organic synthesis has been critically important for the development of this novel structural class of HIV-1 protease inhibitors. We have outlined our synthetic design and execution for these molecular scaffolds that enabled us to design and discover these exceptional inhibitors, including darunavir, the first FDA approved drug for the treatment of patients harboring multidrug-resistant HIV-1 variants. Our new generation of inhibitors includes GRL-14213, which has shown clinical potential and possesses even more structural complexities. The current synthesis enables us to prepare the quantities of this inhibitor necessary for preclinical development. We hope our molecular design and synthetic efforts highlighted in this review will further stimulate drug design and discovery efforts for new and improved medicines.

Acknowledgements

Financial support of this research by the National Institutes of Health (GM53386) and Purdue University is gratefully acknowledged.

Biographies

Arun K. Ghosh obtained his PhD in 1985 at the University of Pittsburgh. He pursued postdoctoral research at Harvard University (1985–1988). He was a research fellow at Merck Research Laboratories. In 1994, he joined the chemistry faculty at the University of Illinois-Chicago as an assistant Professor and became full Professor in 1998. In 2005, he moved to

Purdue University where he is currently the Ian P. Rothwell Distinguished Professor in the Department of Chemistry and Department of Medicinal Chemistry and Molecular Pharmacology. His particular interests include: exploration of chemistry and biology of bioactive natural products, development of tools and strategies for protein structure-based molecular design, drug-discovery and development of new reactions and their applications.

Margherita Brindisi obtained her BS in Chemistry and Pharmaceutical Technologies cum laude in 2004 at the University of Siena, Italy, where she also received her Ph.D. in Pharmaceutical Sciences in 2008. She then pursued her postdoctoral studies at Purdue University, West Lafayette (2010–2011 and 2016–2017) in Professor Ghosh's laboratories. She worked on the design and synthesis of protease inhibitors for the treatment of HIV-AIDS and Alzheimer's disease. She is currently a researcher at the University of Siena at the Department of Biotechnology, Chemistry, and Pharmacy. Her research interests are focused on the development of novel treatments for cancer, pain, parasitic diseases, and brain disorders.

Abbreviations

AIBN	<i>Azobisisobutyronitrile</i>
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy <i>bis</i> -THF, <i>bis</i> -Tetrahydrofuran
Boc	<i>tert</i> -Butyloxycarbonyl
CNS	Central Nervous System
<i>m</i>-CPBA	<i>meta</i> -Chloroperoxybenzoic acid
<i>Cp</i>-THF	Cyclopentyl-tetrahydrofuran
<i>Crn</i>-THF	Crown-tetrahydrofuran
CSA	Camphorsulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM	Dichloromethane
DHP	3,4-Dihydro-2 <i>H</i> -pyran
DIBAL	H, Diisobutylaluminium hydride
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DPPA	Diphenylphosphoryl azide
DSC	<i>N,N</i> -disuccinimidyl carbonate
FabF	beta-Ketoacyl-ACP-synthase II
FDA	Food and Drug Administration
FRET	Fluorescence Resonance Energy Transfer
HIV	Human Immunodeficiency Virus
LAH	Lithium aluminum hydride
NBS	<i>N</i> -Bromosuccinimide
NIS	<i>N</i> -Iodosuccinimide
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
PPL	Porcine Pancreatic Lipase
PPTS	Pyridinium <i>p</i> -toluenesulfonate
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBAI	Tetra- <i>n</i> -butylammonium iodide
TBS	<i>tert</i> -Butyldimethylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxidanyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMSCl	Trimethylsilyl chloride
TPAP	Tetrapropylammonium perruthenate

Tp-THF

Tetrahydropyranyl-tetrahydrofuran

References

- [1]. Nicolaou KC, Hale CRH, Natl. Sci. Rev 2014, 1, 233–252.
- [2]. Hoffmann RW, Angew. Chem. Int. Ed 2013, 52, 123–130; Angew. Chem. 2013, 125, 133–140.
- [3]. Matlin SA, Abegaz BM, Chemistry for Development. In The Chemical Element: Chemistry's Contribution to Our Global Future, 1st ed., Wiley-VCH, Weinheim, 2011.
- [4]. Ghosh AK, Gemma S, Structure-based Design of Drugs and other Bioactive Molecules-Tools and Strategies, Wiley-VCH, Weinheim, 2014.
- [5]. MuÇoz-Torrero D, Mangoni AA, Liu H, Hulme C, Rautio J, Karaman R, de Sousa ME, Prokai-Tatrai K, Sabatier JM, Siciliano C, Luque FJ, Kokotos G, Ragno R, Collina S, Guillou C, Gutschow M, Agrofoglio LA, Molecules 2018, 23, 65.
- [6]. Eder J, Sedrani R, Wiesmann C, Nat. Rev. Drug. Discov 2014, 13, 577–587. [PubMed: 25033734]
- [7]. Ghosh AK, J. Med. Chem 2009, 52, 2163–2176. [PubMed: 19323561]
- [8]. Ghosh AK, J. Org. Chem 2010, 75, 7967–7989. [PubMed: 20936876]
- [9]. Ghosh AK, Chen ZH, Effenberger KA, Jurica MS, J. Org. Chem 2014, 79, 5697–5709. [PubMed: 24873648]
- [10]. Nguyen TL, Xu X, Gussio R, Ghosh AK, Hamel E, J. Chem. Inf. Model 2010, 50, 2019–2028. [PubMed: 21028850]
- [11]. Zhang YW, Ghosh AK, Pommier Y, Cell Cycle 2012, 11, 4424–4435. [PubMed: 23159859]
- [12]. Pryor DE, O'Brate A, Bilcer G, Diaz JF, Wang Y, Kabaki M, Jung MK, Andreu JM, Ghosh AK, Giannakakou P, Hamel E, Biochemistry 2002, 41, 9109–9115. [PubMed: 12119025]
- [13]. Greene WC, Eur. J. Immunol 2007, 37, S94–S102. [PubMed: 17972351]
- [14]. Gilbert MT, Rambaut A, Wlasiuk G, Spira TJ, Pitchenik AE, Worobey M, Proc. Natl. Acad. Sci. USA 2007, 104, 18566–18570. [PubMed: 17978186]
- [15]. Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dautet C, Axler-Blin C, Vezinet-Brun F, Rouzioux C, Ro-zenbaum W, Montagnier L, Science 1983, 220, 868–871. [PubMed: 6189183]
- [16]. Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF, Palker TJ, Redfield R, Oleske J, Safai B, White G, Foster P, Markham PD, Science 1984, 224, 500–503. [PubMed: 6200936]
- [17]. Sepkowitz KA, Engl N. J. Med 2001, 344, 1764–1772.
- [18]. De Clercq E, J. Med. Chem 2005, 48, 1297–1313. [PubMed: 15743172]
- [19]. Kohl NE, Emini EA, Schleif WA, Davis LJ, Heimbach JC, Dixon RAF, Scholnick EM, Sigal IS, Proc. Natl. Acad. Sci. USA 1988, 85, 4686–4690. [PubMed: 3290901]
- [20]. Graves MC, Lim JJ, Heimer EP, Kramer RA, Proc. Natl. Acad. Sci. USA 1988, 85, 2449–2453. [PubMed: 3282230]
- [21]. Wlodawer A, Vondrasek J, Annu. Rev. Biophys. Biomol. Struct 1998, 27, 249–284. [PubMed: 9646869]
- [22]. Ghosh AK, Osswald HL, Prato G, J. Med. Chem 2016, 59, 5172–5208. [PubMed: 26799988]
- [23]. Hue S, Gifford RJ, Dunn D, Fernhill E, Pillay D, J. Virol 2009, 83, 2645–2654. [PubMed: 19158238]
- [24]. Roberts NA, Martin JA, Kinchington D, Broadhurst AV, Craig JC, Duncan IB, Galpin SA, Handa BK, Kay J, Krohn A, Science 1990, 248, 358–361. [PubMed: 2183354]
- [25]. Duncan IB, Redshaw S, Discovery and Early Development of Saquinavir in Protease inhibitors in AIDS Therapy, Marcel Dekker, New York 2001.
- [26]. Mitsuya H, Maeda K, Das D, Ghosh AK, Adv. Pharmacol 2008, 56, 169–197. [PubMed: 18086412]
- [27]. Flexner C, Engl N. J. Med 1998, 338, 1281–1292.
- [28]. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV, Mehendale S, Chariyalertsak S, Santos BR,

Mayer KH, Hoffman IF, Eshleman SH, Piwowar-Manning E, Wang L, Makhema J, Mills LA, de Bruyn G, Sanne I, Eron J, Gallant J, Havlir D, Swindells S, Ribaudo H, Elharrar V, Burns D, Taha TE, Nielsen-Saines K, Celentano D, Essex M, Fleming TR, Engl N. *J. Med* 2011, 365, 493–505.

- [29]. Dieffenbach CW, Fauci AS, *Ann. Intern. Med* 2011, 154, 766–771. [PubMed: 21628350]
- [30]. Krohn A, Redshaw S, Ritchie JC, Graves BJ, Hatada MH, *J. Med. Chem* 1991, 34, 3340–3342. [PubMed: 1956054]
- [31]. Hong L, Zhang XC, Hartsuck JA, Tang J, *Protein Sci.* 2000, 9, 1898–1904. [PubMed: 11106162]
- [32]. Cihlar T, Fordyce M, *Curr. Opin. Virol* 2016, 18, 50–56. [PubMed: 27023283]
- [33]. Patel K, Hernan MA, Williams PL, Seeger JD, McIntosh K, Van Dyke RB, Seage GR III, *Clin. Infect. Dis* 2008, 46, 507–515. [PubMed: 18199042]
- [34]. Ghosh AK, Chapsal B, Mitsuya H, Darunavir, a New PI with Dual Mechanism: From a Novel Drug Design Concept to New Hope Against Drug-Resistant HIV In ‘Aspartic Acid Proteases as Therapeutic Targets, Wiley-VCH, Weinheim, 2010.
- [35]. Ghosh AK, Dawson ZL, Mitsuya H, *Bioorg. Med. Chem* 2007, 15, 7576–7580. [PubMed: 17900913]
- [36]. Koh Y, Nakata H, Maeda K, Ogata H, Bilcer G, Devasamudram T, Kincaid JF, Boross P, Wang YF, Tie Y, Volarath P, Gaddis L, Harrison RW, Weber IT, Ghosh AK, Mitsuya H, *Antimicrob. Agents Chemother* 2003, 47, 3123–3129. [PubMed: 14506019]
- [37]. Deeks ED, *Drugs* 2014, 74, 99–125. [PubMed: 24338166]
- [38]. Curran A, Ribera Pascuet E, *Enferm. Infecc. Microbiol. Clin* 2008, 26, 14–22.
- [39]. Ghosh AK, Chapsal BD in *From Introduction to Biological and Small Molecule Drug Research and Development* (Eds.: Ganellin CR, Roberts SM, Jefferis R), 2013, pp. 355–384.
- [40]. Ghosh AK, Anderson DD, Weber IT, Mitsuya H, *Angew. Chem. Int. Ed* 2012, 51, 1778–1802; *Angew. Chem.* 2012, 124, 1812–1838.
- [41]. Ghosh AK, Sridhar PR, Leshchenko S, Hussain AK, Li J, Kova-levsky AY, Walters DE, Wedekind JE, Grum-Tokars V, Das D, Koh Y, Maeda K, Gatanaga H, Weber IT, Mitsuya H, *J. Med. Chem* 2006, 49, 5252–5261. [PubMed: 16913714]
- [42]. Ghosh AK, Xu CX, Rao KV, Baldrige A, Agniswamy J, Wang YF, Weber IT, Aoki M, Miguel SG, Amano M, Mitsuya H, *ChemMedChem* 2010, 5, 1850–1854. [PubMed: 20827746]
- [43]. Aoki M, Hayashi H, Rao KV, Das D, Higashi-Kuwata N, Bulut H, Aoki-Ogata H, Takamatsu Y, Yedidi RS, Davis DA, Hattori SI, Nishida N, Hasegawa K, Takamune N, Nyalapatla PR, Osswald HL, Jono H, Saito H, Yarchoan R, Misumi S, Ghosh AK, Mitsuya H, *Elife* 2017, 6, e28020. [PubMed: 29039736]
- [44]. Ghosh AK, Rao KV, Nyalapatla PR, Kovala S, Brindisi M, Osswald HL, Sekhara Reddy B, Agniswamy J, Wang YF, Aoki M, Hattori SI, Weber IT, Mitsuya H, *ChemMedChem* 2018, 13, 803–815. [PubMed: 29437300]
- [45]. Ghosh AK, Rao KV, Nyalapatla PR, Osswald HL, Martyr CD, Aoki M, Hayashi H, Agniswamy J, Wang YF, Bulut H, Das D, Weber IT, Mitsuya H, *J. Med. Chem* 2017, 60, 4267–4278. [PubMed: 28418652]
- [46]. Newman DJ, Cragg GM, *J. Nat. Prod* 2012, 75, 311–335. [PubMed: 22316239]
- [47]. Haustedt LO, Mang C, Siems K, Schiewe H, *Curr. Opin. Drug. Discov. Devel* 2006, 9, 445–462.
- [48]. Ganesan A, *Curr. Opin. Chem. Biol* 2008, 12, 306–317. [PubMed: 18423384]
- [49]. Clardy J, Walsh C, *Nature* 2004, 432, 829–837. [PubMed: 15602548]
- [50]. Li JW, Vederas JC, *Science* 2009, 325, 161–165. [PubMed: 19589993]
- [51]. Kingston DG, *J. Nat. Prod* 2011, 74, 496–511. [PubMed: 21138324]
- [52]. Li DAK, Meujo DA, Hamann MT, *Expert Opin. Drug Discovery* 2009, 4, 109–146.
- [53]. Zanno P, Miura I, Nakanishi K, Elder DL, *J. Am. Chem. Soc* 1975, 97, 1975–1977. [PubMed: 1133406]
- [54]. Nakanishi K, *Bioorg. Med. Chem* 2005, 13, 4987–5000. [PubMed: 15990319]
- [55]. Palanichamy K, Kaliappan KP, *Chem. Asian J* 2010, 5, 668–703. [PubMed: 20209576]

- [56]. Singh SB, Ondeyka JG, Herath KB, Zhang C, Jayasuriya H, Zink DL, Parthasarathy G, Becker JW, Wang J, Soisson SM, Bioorg. Med. Chem. Lett 2009, 19, 4756–4759. [PubMed: 19581087]
- [57]. Noble S, Faulds D, Drugs 1996, 52, 93–112. [PubMed: 8799687]
- [58]. Kitchen VS, Skinner C, Ariyoshi K, Lane EA, Duncan IB, Burckhardt J, Burger HU, Bragman K, Pinching AJ, Weber JN, Lancet 1995, 345, 952–954. [PubMed: 7715294]
- [59]. Kempf DJ, Marsh KC, Denissen JF, McDonald E, Vasavanonda S, Flentge CA, Green BE, Fino L, Park CH, Kong XP, Proc. Natl. Acad. Sci. USA 1995, 92, 2484–2488. [PubMed: 7708670]
- [60]. Vacca JP, Dorsey BD, Schleif WA, Levin RB, McDaniel SL, Darke PL, Zugay J, Quintero JC, Blahy OM, Roth E, Sardana VV, Schlabach AJ, Graham PI, Condra JH, Gotlib L, Holloway MK, Lin J, Chen IW, Vastag K, Ostovic D, Anderson PS, Emini EA, Huff JR, Proc. Natl. Acad. Sci. USA 1994, 91, 4096–4100. [PubMed: 8171040]
- [61]. Kaldor SW, Kalish VJ, Davies JF II, Shetty BV, Fritz JE, Appelt K, Burgess JA, Campanale KM, Chirgadze NY, Clawson DK, Dressman BA, Hatch SD, Khalil DA, Kosa MB, Lubbehusen PP, Muesing MA, Patick AK, Reich SH, Su KS, Tatlock JH, J. Med. Chem 1997, 40, 3979–3985. [PubMed: 9397180]
- [62]. Kim EE, Baker CT, Dwyer MD, Murcko MA, Rao BG, Tung RD, Navia MA, J. Am. Chem. Soc 1995, 117, 1181–1182.
- [63]. Sham HL, Kempf DJ, Molla A, Marsh KC, Kumar GN, Chen CM, Kati W, Stewart K, Lal R, Hsu A, Betebenner D, Korneyeva M, Vasavanonda S, McDonald E, Saldivar A, Wideburg N, Chen X, Niu P, Park C, Jayanti V, Grabowski B, Granneman GR, Sun E, Japour AJ, Leonard JM, Plattner JJ, Norbeck DW, Antimicrob. Agents Chemother 1998, 42, 3218–3224. [PubMed: 9835517]
- [64]. Bold G, Fässler A, Capraro HG, Cozens R, Klimkait T, Lazdins J, Mestan J, Poncioni B, Rçsel J, Stover D, Tintelnot-Blomley M, Acemoglu F, Beck W, Boss E, Eschbach M, Hürlimann T, Masso E, Roussel S, Ucci-Stoll K, Wyss D, Lang M, J. Med. Chem 1998, 41, 3387–3401. [PubMed: 9719591]
- [65]. Doyon L, Tremblay S, Bourgon L, Wardrop E, Cordingley MG, Antiviral Res. 2005, 68, 27–35. [PubMed: 16122817]
- [66]. Tie Y, Kovalevsky AY, Boross P, Wang YF, Ghosh AK, Tozser J, Harrison RW, Weber IT, Proteins 2007, 67, 232–242. [PubMed: 17243183]
- [67]. Ghosh AK, Shin D, Swanson L, Krishnan K, Cho H, Hussain KA, Walters DE, Holland L, Buthod J, Farmaco 2001, 56, 29–32. [PubMed: 11347961]
- [68]. Ghosh AK, Kincaid JF, Cho W, Walters DE, Krishnan K, Hussain KA, Koo Y, Cho H, Rudall C, Holland L, Buthod J, Bioorg. Med. Chem. Lett 1998, 8, 687–690. [PubMed: 9871583]
- [69]. Gulnik SV, Suvorov LI, Liu B, Yu B, Anderson B, Mitsuya H, Erickson JW, Biochemistry 1995, 34, 9282–9287. [PubMed: 7626598]
- [70]. Yoshimura K, Kato R, Kavlick MF, Nguyen A, Maroun V, Maeda K, Hussain KA, Ghosh AK, Gulnik SV, Erickson JW, Mitsuya H, J. Virol 2002, 76, 1349–1358. [PubMed: 11773409]
- [71]. Koh Y, Matsumi S, Das D, Amano M, Davis DA, Li J, Leschenko S, Baldrige A, Shioda T, Yarchoan R, Ghosh AK, Mitsuya H, J. Biol. Chem 2007, 282, 28709–28720. [PubMed: 17635930]
- [72]. FDA approves Darunavir on June 23, 2006: FDA approved new HIV treatment for patients who do not respond to existing drugs. Please see <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01395.html>.
- [73]. Ghosh AK, Duong TT, McKee SP, Tetrahedron Lett. 1991, 32, 4251–4254. [PubMed: 30853726]
- [74]. Ghosh AK, Leshchenko S, Noetzel M, J. Org. Chem 2004, 69, 7822–7829. [PubMed: 15527257]
- [75]. Ghosh AK, Martyr CD, (Eds.: Li JJ, Johnson DS), Wiley, 2010, pp. 29–44.
- [76]. Ghosh AK, Kincaid JF, Walters DE, Chen Y, Chaudhuri NC, Thompson WJ, Culberson C, Fitzgerald PM, Lee HY, McKee SP, Munson PM, Duong TT, Darke PL, Zugay JA, Schleif WA, Axel MG, Lin J, Huff JR, J. Med. Chem 1996, 39, 3278–3290. [PubMed: 8765511]
- [77]. Ghosh AK, Chen Y, Tetrahedron Lett. 1995, 36, 505–508. [PubMed: 30310245]
- [78]. Ghosh AK, Kawahama R, Tetrahedron Lett. 1999, 40, 1083–1086. [PubMed: 30422132]
- [79]. Lemaire SFE, Horvath A, Aelterman WAA, Rammeloo TJL (Tibotec Pharmaceuticals Ltd., Ireland), WO 2008055970 A2, 2007.

- [80]. Ghosh AK, Li J, Perali RS, Synthesis 2006, 3015–3018. [PubMed: 30443083]
- [81]. Ghosh AK, Martyr CD, Steffey M, Wang YF, Agniswamy J, Amano M, Weber IT, Mitsuya H, ACS Med. Chem. Lett 2011, 2, 298–302. [PubMed: 22509432]
- [82]. Ghosh AK, Thompson WJ, Holloway MK, McKee SP, Duong TT, Lee HY, Munson PM, Smith AM, Wai JM, Darke PL, Zugay JA, Emini EA, Schleif WA, Huff JR, Anderson PS, J. Med. Chem 1993, 36, 2300–2310. [PubMed: 8360874]
- [83]. Ghosh AK, Bilcer G, Schiltz G, Synthesis 2001, 2203–2229. [PubMed: 30393404]
- [84]. Deardorff DR, Windham CQ, Craney CL, Org. Synth 1998, 9, 487–492.
- [85]. Ghosh AK, Takayama J, Tetrahedron Lett. 2008, 49, 3409–3412. [PubMed: 18548130]
- [86]. Amano M, Tojo Y, Salcedo-Gomez PM, Campbell JR, Das D, Aoki M, Xu CX, Rao KV, Ghosh AK, Mitsuya H, Antimicrob. Agents Chemother 2013, 57, 2036–2046. [PubMed: 23403426]
- [87]. Ghosh AK, Xu C-X, Osswald HL, Tetrahedron Lett. 2015, 56, 3314–3317. [PubMed: 26185337]
- [88]. Ghosh AK, Chapsal BD, Weber IT, Mitsuya H, Acc. Chem. Res 2008, 41, 78–86. [PubMed: 17722874]
- [89]. Ghosh AK, Yashchuk S, Mizuno A, Chakraborty N, Agniswamy J, Wang YF, Aoki M, Gomez PM, Amano M, Weber IT, Mitsuya H, Chem-MedChem 2015, 10, 107–115.
- [90]. Salcedo Gómez PM, Amano M, Yashchuk S, Mizuno A, Das D, Ghosh AK, Mitsuya H, Antimicrob. Agents Chemother 2013, 57, 6110–6121. [PubMed: 24080647]
- [91]. Ghosh AK, Martyr CD, Osswald HL, Sheri VR, Kassekert LA, Chen S, Agniswamy J, Wang YF, Hayashi H, Aoki M, Weber IT, Mitsuya H, J. Med. Chem 2015, 58, 6994–7006. [PubMed: 26306007]
- [92]. Ghosh AK, Martyr CD, Kassekert LA, Nyalapatla PR, Steffey M, Agniswamy J, Wang YF, Weber IT, Amano M, Mitsuya H, Org. Biomol. Chem 2015, 13, 11607–11621. [PubMed: 26462551]
- [93]. Yang YY, Xu J, You ZW, Xu XH, Qiu XL, Qing FL, Org. Lett 2007, 9, 5437–5440. [PubMed: 18020349]
- [94]. Yang YY, Meng WD, Qing FL, Org. Lett 2004, 6, 4257–4259. [PubMed: 15524457]
- [95]. Dueno EE, Chu F, Kim S-I, Jung KW, Tetrahedron Lett. 1999, 40, 1843–1846.
- [96]. Brückner R, Priepke H, Angew. Chem. Int. Ed. Engl 1988, 27, 278–280; Angew. Chem. 1988, 100, 285–286.
- [97]. Swamy KC, Kumar NN, Balaraman E, Kumar KV, Chem. Rev 2009, 109, 2551–2651. [PubMed: 19382806]
- [98]. Ghosh AK, Gemma S, Takayama J, Baldrige A, Leshchenko-Yash-chuk S, Miller HB, Wang YF, Kovalevsky AY, Koh Y, Weber IT, Mitsuya H, Org. Biomol. Chem 2008, 6, 3703–3713. [PubMed: 18843400]
- [99]. Ghosh AK, Gemma S, Baldrige A, Wang YF, Kovalevsky AY, Koh Y, Weber IT, Mitsuya H, J. Med. Chem 2008, 51, 6021–6033. [PubMed: 18783203]
- [100]. Ghosh AK, Parham GL, Martyr CD, Nyalapatla PR, Osswald HL, Agniswamy J, Wang YF, Amano M, Weber IT, Mitsuya H, J. Med. Chem 2013, 56, 6792–6802. [PubMed: 23947685]
- [101]. Ghosh AK, Chapsal BD, Baldrige A, Steffey MP, Walters DE, Koh Y, Amano M, Mitsuya H, J. Med. Chem 2011, 54, 622–634. [PubMed: 21194227]
- [102]. Nakashima H, Masayuki S, Taniguchi T, Ogasawara K, Synthesis 2000, 817–823.
- [103]. Ishihara K, Kurihara H, Yamamoto H, J. Org. Chem 1993, 58, 3791–3793.
- [104]. Ghosh AK, Sarkar A, Tetrahedron Lett. 2017, 58, 3230–3233. [PubMed: 29200514]
- [105]. Von Langen DJ, Tolman RL, Tetrahedron: Asymmetry 1997, 8, 677–681.
- [106]. Grieco PA, Gilman S, Nishizawa M, J. Org. Chem 1976, 41, 1485–1486.
- [107]. Mukherjee S, Corey EJ, Org. Lett 2010, 12, 1024–1027. [PubMed: 20131879]
- [108]. Mahender Reddy K, Bhimireddy E, Thirupathi B, Breitler S, Yu S, Corey EJ, J. Am. Chem. Soc 2016, 138, 2443–2453. [PubMed: 26812167]
- [109]. Nicolaou KC, Adsool VA, Hale CR, Org. Lett 2010, 12, 1552–1555. [PubMed: 20192259]
- [110]. Katsuki T, Sharpless KB, J. Am. Chem. Soc 1980, 102, 5974–5976.

- [111]. Gao Y, Hanson RM, Klunder JM, Ko SY, Masamune H, Sharpless KB, J. Am. Chem. Soc 1987, 109, 5765–5780.
- [112]. Caron M, Carlier K, Sharpless KB, J. Org. Chem 1988, 53, 5185–5187.
- [113]. Ghosh AK, McKee SP, Lee HY, Thompson WT, J. Chem. Soc. Chem. Commun 1992, 273–274. [PubMed: 30319147]
- [114]. Ghosh AK, Cardenas EL, Brindisi M, Tetrahedron Lett. 2017, 58, 4062–4065. [PubMed: 29335658]

Figure 1. Structures of saquinavir (**1**) and saquinavir-bound HIV-1 protease, darunavir (**2**) and GRL-14213 (**3**).

Figure 2. Structure of monensin (4), azadirachtin (5), ginkgolide (6), and platensimycin (7) natural products.

Figure 3.
Structures of *bis*-THF containing HIV-1 protease inhibitors.

Figure 4.
Structures of *bis*-THF-derived HIV-1 protease inhibitors **10** and **11** and darunavir (**2**).

Figure 5.
Structures of polycyclic ether-containing potent HIV-1 protease inhibitors.

Figure 6.
Cp-THF-containing novel PIs.

Figure 7.
Tris-THF containing inhibitors.

Figure 8.
1,6-Dioxatriquinane-containing inhibitors.

Figure 9.
gem-Difluoro- and amino-*bis*-THF containing inhibitors.

Figure 10.
Tp-THF containing inhibitor **13**.

Figure 11.
Ccm-THF containing inhibitor **3**.

Scheme 1.
Retrosynthetic analysis for darunavir synthesis.

Scheme 2.
Darunavir (**2**) assembly.

Scheme 3.
Diethyl malate derived synthesis of *bis*-THF ligand (-)-**17**.

Scheme 4.

Optically active synthesis of the *bis*-THF ligand **(-)-17** from 2,3-dihydrofuran.

Scheme 5. Stereoselective photochemical 1,3-dioxolane addition route to *bis*-THF alcohol (-)-17.

Scheme 6. Synthesis of *bis*-THF alcohol (**(-)-17**) using a multi-component reaction.

Scheme 7. Asymmetric *anti*-aldol route to *bis*-THF alcohol **(-)-17**.

Scheme 8. Synthesis of *bis*-THF ligand **(-)-17** involving a [2,3]-sigmatropic rearrangement.

Scheme 9. Asymmetric synthesis of azido epoxide **51** and Boc-amino epoxide **20**.

Scheme 10.
Synthesis of epoxide **20** from phenylalanine.

Scheme 11.

Synthesis *Cp*-THF alcohol **58** involving an enzymatic asymmetrization step.

Scheme 12. Enantioselective synthesis of *Cp*-THF alcohol **58** from lactone **59**.

Scheme 13.
First bromohydrin route to *Cp*-THF alcohol **58**.

Scheme 14.
Second bromohydrin route to *Cp*-THF alcohol **58**.

Scheme 15.
Synthesis of the *SSS*-type oxatricyclic *Tris*-THF ligand **71**.

Scheme 16. Synthesis of the *SAS*-type oxatricyclic *Tris*-THF ligand **77**.

Scheme 17.

Synthesis of the *SSS* and *SAS* dioxatriquinane ligands **85** and **87**.

Scheme 18.
Synthesis of Weinreb amide derivatives **93** and **94**.

Scheme 19.
Synthesis of *gem*-difluoro derivative of *bis*-THF **97**.

Scheme 20.

Stereoselective synthesis of C-4 isopropylamino *bis*-THF derivative **105**.

Scheme 21. First synthesis of *Tp*-THF ligand **109**.

Scheme 22.A novel approach to *Tp*-THF ligand **109**.

Scheme 23.
Synthesis of *Crn*-THF ligand **122**.

Scheme 24.
Synthesis of difluoroazidoepoxide **126**.

Scheme 25. Curtius rearrangement in the synthesis of key difluoro epoxide **130**.

Scheme 26. Synthesis of fluoroisosteric amine **134** and of final compound GRL-14213 (**3**).