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Syntheses of FDA Approved HIV Protease Inhibitors

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Abstract

The treatment of HIV and AIDS was revolutionized by the introduction of peptidomimetic aspartyl protease inhibitors. One of the major limitations of this type of therapy is that higher therapeutic doses are necessary because of the presence of ‘peptide-like’ features in the drugs. Therefore, adequate supplies and cost effective syntheses of these drugs are of utmost importance. To date, there are six protease inhibitors approved by the United States Food and Drug Administration (FDA) for the treatment of HIV and AIDS. This review focuses on the published syntheses of currently FDA approved HIV protease inhibitor drugs, their isosteres and ligands.

Keywords

HIV; protease; inhibitor; isostere; synthesis

1 Introduction

Acquired immunodeficiency syndrome (AIDS), a degenerative disease of the immune system, is one of the most challenging problems in medicine. The Centers for Disease Control estimated that at the end of 2000, there were 36.1 million people living with the disease and an estimated 21.8 million have died since the beginning of the epidemic, 3 million in the year 2000 alone. Among various strategies to combat this devastating disease, therapeutic inhibition of the virally encoded HIV protease became an attractive target.[1] During viral replication, gag and gagpol gene products are translated as precursor polyproteins. These proteins are processed by a virally encoded pro-tease to provide structural proteins (p 17, p 24, p 9, and p7) and essential viral enzymes (including protease, reverse transcriptase, and integrase).[2] The virally encoded pro-tease has been characterized as a homodimeric endopeptidase of the aspartyl protease family.[3]

Based on the transition state mimetic concept utilizing various nonhydrolyzable hydroxyethylene and hydroxyethylamine isosteres, an impressive number of potent and selective HIV protease inhibitors have been developed.[1,4] The clinical effectiveness of combination therapy consisting of protease inhibitors and reverse transcriptase inhibitors has now been well documented.[5] These treatment regimens have changed the course of HIV management and the progression of AIDS.[6] One of the major limitations of the current therapy is that higher therapeutic doses are necessary because of the presence of ‘peptide-like’ features in the drugs. Consequently, adequate supplies and cost effective syntheses of these drugs are of utmost importance. To date, there are six protease inhibitors approved by

the United States Food and Drug Administration, (FDA) for the treatment of HIV and AIDS. All of these inhibitor drugs contain multiple stereocenters, complex heterocycles and rare functionalities. No doubt, large scale synthesis in enantiomerically pure form posed considerable challenges as well as opportunities for organic synthesis. An incredible effort has been carried out by academic and pharmaceutical laboratories in the area of design and synthesis of HIV protease inhibitors. It is beyond the scope of this review to cover all the synthetic work in this area. This review is intended to focus on the syntheses of current FDA approved inhibitor drugs, their isosteres and ligands. Herein, we report a full review of the published syntheses of these important therapeutics.

2 Saquinavir (Invirase®, Fortovase®, Ro 31–8959)

In December 1995, the FDA approved the first HIV pro-tease inhibitor for the treatment of AIDS, saquinavir (tradenames Invirase®, Fortovase®). Saquinavir (**1**, Figure 1), discovered by Hoffman-La Roche, displays an IC_{50} value of 2 nM and a K_i value at pH 5.5 of 0.12 nM against HIV-1; moreover, it is a very selective inhibitor of the HIV protease, showing less than 50% inhibition of the other aspartic proteases found in humans.[7]

Most syntheses of saquinavir (**1**) utilize a convergent strategy based on the following disconnections: (i) carboxylic acid moiety **2**, which can be derived from quinaldic acid (**5**) and l-asparagine (**6**), (ii) an electrophilic amino alcohol equivalent such as l-phenylalanine-based isostere **3** and (iii) decahydroisoquinoline derivative **4** (Figure 2).

2.1 Synthesis of the Saquinavir Isostere

An early synthesis of the saquinavir isostere by scientists at Roche began with benzyloxycarbonyl (Cbz) protected l-phenylalanine (**7**) which was transformed into corresponding chloromethyl ketone **8** using established procedures (Scheme 1).[8] Chloromethyl ketone **8** was then reduced with $NaBH_4$ to afford a 3:1 mixture of diastereomers in favor of the desired (*S*)-alcohol (**9**) which was separated from the minor (*R*)-isomer. To complete the isostere synthesis, epoxide **10** was formed by the reaction of KOH with chloroalcohol **9**.[9]

A number of other methods have been developed to produce an *N*-protected form of (2*S*, 3*S*)-amino epoxide **10**, with azidoepoxides being the most common targets. In 1993, Ghosh and co-workers published an efficient synthesis of azidoepoxide **15** utilizing Sharpless asymmetric epoxidation (SAE).[10] Their first step was the copper cyanide-catalyzed addition of phenylmagnesium bromide to oxirane **11**, which provided allylic alcohol **12** in 97% yield. This was followed by SAE using (−)-diethyl-D-tartrate [(−)-DET] which afforded epoxide **13** in 64% yield (Scheme 2). Regioselective epoxide ring opening with $[Ti(O\textit{i}\text{-}Pr)_2(N_3)_2]$, which was prepared in situ by refluxing $Ti(O\textit{i}\text{-}Pr)_4$ and Me_3SiN_3 in benzene for 5 hours,[11] provided azidodiol **14** in 96% yield. Finally, epoxide **15** was formed in 86% yield by treatment of **14** with 2-acetoxy-isobutyryl chloride followed by excess NaOMe.

An alternative synthesis published by Bennet et al. also utilizes SAE to introduce chirality into the molecule, but uses a slightly different procedure for forming the allylic alcohol.[12] In their synthesis, phenylacetaldehyde (**16**) is subjected to Horner–Emmons homologation with

triethylphosphonoacetate to afford *E*-unsaturated ester **17** which was subsequently reduced using diisobutylaluminum hydride (Dibal-H) to provide allylic alcohol **12** (Scheme 3). The corresponding azidodiol (**14**) was produced by a similar sequence of reactions as the Ghosh synthesis above. Reaction of **14** with *p*-toluenesulfonyl chloride (TsCl) followed by NaH produced azidoepoxide **15** in 70% yield.

Ghosh and co-workers have also prepared azidoepoxide **15** starting instead from diethyl-D-tartrate.[13] Thus, reduction of benzylidene protected (−)-DET (**18**)[14] with lithium aluminum hydride (LAH) and $AlCl_3$ gave the corresponding benzyl protected triol, which was protected as the corresponding acetonide with acetone and catalytic *p*-toluenesulfonic acid (TsOH) to afford alcohol **19** in 88% yield over 2 steps (Scheme 4).[15] Epoxide **20** was produced in 77% yield by removal of the *O*-benzyl protecting group with $Pd(OH)_2$ (Pearlman's Catalyst) and H_2 followed by Mitsunobu condensation of the resulting 1,2-diol with triphenylphosphine and diethylazodicarboxylate (DEAD). Copper cyanide-catalyzed addition of phenyl-magnesium bromide regioselectively produced alcohol **21** in 93% yield. Mitsunobu azidation of the resulting alcohol with PPh_3, diphenylphosphoryl azide (DPPA) and DEAD afforded the corresponding protected azide, which was deprotected with 40% aqueous acetic acid to furnish azidodiol **14** in 64% yield over 2 steps.[16] The desired azidoepoxide (**15**) was synthesized in 72% yield using 2-acetyoxyisobutyryl chloride followed by excess NaOMe, while the diastereomeric epoxide (**22**) was produced via successive treatment of **14** with benzoyl chloride (BzCl), $MeSO_2Cl$ (MsCl) and NaOMe in 66% yield.

Several different synthetic equivalents of **15** have been developed with *t*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz) protected amino epoxides being quite common. As shown in Scheme 5, *N*-Boc-l-phenylalanine (**23a**) and *N*-Cbz-l-phenylalanine (**23b**) were treated with carbonyldiimidazole (CDI) followed by the magnesium enolate of malonic acid monoester to afford -keto esters **24a** and **24b**, respectively.[17] Sodium borohydride reduction of **24a** and **24b** afforded 3:1 mixtures of diastereomers with the desired (*R*)-alcohols being the major products.[9] After separation, protection as the corresponding acetonide using 2,2-dimethoxypropane (DMP) and TsOH was followed by NaOH hydrolysis to afford acids **25a** and **25b**. Treatment of the resulting acids with oxalyl chloride produced the corresponding acid chlorides. Conversion to bromides **26a** and **26b** was accomplished via the Barton decarboxylative bromination reaction utilizing 2-mercaptopyridine *N*-oxide sodium salt.[18] Bromides **26a** and **26b** were then deprotected with glacial acetic acid and concentrated HCl followed by cyclization with methanolic KOH to afford epoxides **27a** and **27b**.

Another approach to *N*-protected epoxides involved the use of tris-((trimethylsilyl)oxy)ethene (**29**).[19] In this synthesis,[9] treatment of *N*-phthalyl protected acid chloride **28** with 2 equivalents of tris-((trimethylsilyl)oxy)ethene (**29**) at 95–100 °C followed by aqueous HCl produced α-hydroxymethyl ketone **30** in 63% yield (Scheme 6). Protection of the alcohol as a tetrahydropyranyl (THP) ether using dihydropyran (DHP) and a catalytic amount of TsOH followed by reduction of the ketone with $NaBH_4$ produced alcohol **31**. Mesylation with MsCl followed by removal of the THP group using TsOH gave the

corresponding mesylate in 29% yield from **30**. Epoxide ring formation was accomplished by treatment with *t*-BuOK, which afforded **32** in 69% yield.

An alternative synthetic equivalent of **15** was produced by formation of an α-hydroxy aldehyde **36**, which can then undergo a reductive coupling with decahydroisoquinoline derivative **4** using $NaCNBH_3$.[9] In the event, *N*-Boc-protected L-phenylalanal (**33**) was reacted with 2-(trimethylsilyl)thiazole followed by desilylation with tetrabutylammonium fluoride (TBAF) to give a mixture of diastereomeric alcohols (**34**) and (**35**) in a ratio of approximately 2:3 (Scheme 7). Methylation of the thiazole nitrogen followed by $NaBH_4$ reduction and hydrolysis of the thiazolidine using $HgCl_2$ gave α-hydroxy aldehyde **36**. This compound was then coupled with **4** in the presence of $NaCNBH_3$ to produce **37** in 56% overall yield from **34**.

An improved method for preparing an electrophilic hydroxyamine equivalent starting from an acid chloride was published by Göhring et al. in 1996.[20] Starting with *N*-phthalyl-l-phenylalanine (38), conversion to the acid chloride with phosgene followed by reduction with H_2 and Pd/C produced aldehyde 39 (Scheme 8). Interestingly, the use of bases such as triethylamine and lutidine in the Rosenmund reaction led to high degrees of racemization, therefore, butylene oxide was used to neutralize the HCl produced during the reaction. Formation of cyanide 40 was accomplished using NaCN and led to a 3:1 mixture of diastereomers in favor of the (*S*)-alcohol which, when treated with HCl and methanol, yielded hydroxyester 41. After removing the phthalyl group using methylamine and HCl, oxazolidinone 42 was produced by reaction of the aminoalcohol with $COCl_2$ followed by reduction of the ester using $NaBH_4$. Reaction of oxizolidinone 42 with *p*-nitrobenzenesulfonyl chloride (NosCl) afforded nosylate 43 in 40% overall yield from phenylalanine.

An alternative procedure was developed which eliminated the need for phosgene and also reduced the number of steps required. In this synthesis (also found in Scheme 8), following transformation of cyanide **40** to the corresponding carboxylic acid using HCl and water, oxazolidinone **44** was produced by reaction with methyl chloroformate.[20] Formation of the methyl ester with MeOH and H_2SO_4 followed by reduction with $NaBH_4$ led to oxazolidinone **42** which was transformed into the nosylate as above, this time in 41% yield from phenylalanine.

The most efficient synthesis of the central isostere containing portion of saquinavir and the one used to produce the large quantities necessary for clinical development, begins with l-phenylalanine (**45**).[20] Construction of the methyl ester using thionyl chloride and methanol followed by treatment with methyl chloroformate resulted in quantitative formation of methyl ester **46** (Scheme 9). A one-pot sequence involving protection of the carbamate group using *n*-BuLi and TMSCl followed by reaction with chloromethyllithium (derived from *n*-BuLi and bromochloromethane) afforded chloromethyl ketone **47** in 76% yield after aqueous workup which also removed the *N*TMS group. Reduction selectivity was improved from the usual 3:1 obtained using $NaBH_4$ to 19:1 by the use of Al(*i*-PrO)$_3$. Therefore, Meerwein–Ponndorf–Verley reduction of chloromethyl ketone **47** using Al(*i*-PrO)$_3$ and *iso*-propanol provided (*S*)-alcohol **48** in 89% yield and with 95% selectivity. Corey reduction of

chloromethyl ketone **47** using a chiral oxazaborolidine catalyst also showed excellent selectivity (95:5) but required reagents deemed too expensive for large-scale production.

Several other approaches to synthetic equivalents of **15** have been used. Starting from azidodiol **14**, reaction with triisopropylbenzenesulfonyl chloride gave the primary arylsulfonyl derivative which was cyclized with KOH to afford epoxide **15** in 34% yield for 2 steps (Scheme 10).[9] Alternatively, azidodiol **14** was reacted with $SOCl_2$ to afford the cyclic sulfite derivative, which was oxidized using $RuCl_3/NaIO_4$ to provide cyclic sulfate **49** in 96% yield over 2 steps. After coupling with decahydroisoquinoline derivative **4**, the cyclic sulfate derivative was hydrolyzed using methanolic sulfuric acid. An advantage of the cyclic sulfate route is its higher reactivity in the coupling reaction with **4**. While epoxides typically required elevated temperatures to react, **49** proceeded to give 69% of azidodecahydroisoquinoline **50** at room temperature.

A method was developed by Reetz and Binder that provides good epoxide diastereoselectivity directly from α-amino aldehydes, which in turn can be derived from their corresponding amino acids.[21] In their procedure it is essential that the nitrogen be doubly protected to afford the non-chelation controlled *syn*-addition product as the major isomer. Beginning with *N,N*-dibenzyl protected l-phenylalanal (**51**), addition of the arsonium ylide (derived from methyltriphenylarsonium tetrafluoroborate and potassium hexamethyldisilylazide (KHMDS)) provided a 90:10 mixture of *syn*:*anti* diastereomers (**52**) and (**53**) in 75% combined yield (Scheme 11). Reaction of these with NaH afforded the corresponding epoxides in 60% overall yield from aldehyde **51**. While these results demonstrate an efficient diastereoselective synthesis of α-amino ep-oxides in 2 steps from their respective aldehydes, the conditions employed and toxicity of arsenic were thought by scientists at Hoffmann–La Roche to be too severe for application in large scale synthesis.[9]

2.2 Synthesis of the Decahydroisoquinoline Fragment of Saquinavir

Several syntheses of the decahydroisoquinoline portion of saquinavir have been published. Houpis et al. published a synthesis in 1993 which begins with *meso* tetrahydrophthalic anhydride (**56**).[22] Hydrolysis with K_2CO_3 and MeOH followed by recrystallization using (+)-ephedrine gave a single enantiomer of acid **57** in approximately 25% yield (2 steps) and >99% *ee* (Scheme 12). Formation of **59** was accomplished in 66% yield from **57** by treating the acid with oxalyl chloride, hydrogenating the resulting compound over Pd/C with 2,6-lutidine, addition of eno-late **58** to the resulting aldehyde, and cyclizing with acetic acid in methanol. Saturation of the conjugated alkene in **59** by hydrogenation over Pd/C in THF followed by reduction of the amide carbonyl using BH_3 DMS and *n*-$PrNH_2$ provided α-amino ester **60** in 77% yield from **59**. Finally, the *t*-butyl amide was installed by reaction of 60 with the aluminum reagent derived from Al(*i*-Bu)$_3$ and *t*-$BuNH_2$ to afford **4** in 70% yield.

Another synthesis of the decahydroisoquinoline fragment begins with l-phenylalanine (**45**), which undergoes a Pictet–Spengler cyclization to produce acid **61** as shown in Scheme 13.[20] Significant racemization took place during this reaction which required purification via the *p*-TsOH salt. Protection of the amine as the benzyl carbamate followed by displacement of the mixed carbonate (derived from *iso*-butyl chloroformate) with *t*-$BuNH_2$ provided amide

62. Removal of the Cbz group using H_2 and Pd/C followed by dearomatization with a Rh/C catalyst at elevated H_2 pressure led to decahydroisoquinoline **4** in 17–20% overall yield from phenylalanine.

An improved synthesis of decahydroisoquinoline fragment **4** was developed by Hipert and co-workers at Hoffmann–La Roche which decreased the number of steps to 3 and increased the yield to 46%.[20] Beginning with l-phenylalanine (**45**), Pictet–Spengler cyclization using highly concentrated HCl in formaldehyde proceeded with very little racemization to provide acid 61 in 70% yield after recrystallization of the free amino acid to assure enantiopurity (Scheme 14). Amide **63** was formed in 80% yield by reaction of **61** with $COCl_2$ followed by *t*-$BuNH_2$. Finally, hydrogenation at high temperature and pressure with a Ru catalyst afforded **4** in up to 85% yield and with 94% selectivity to complete the synthesis of the decahydroisoquinoline fragment.

2.3 Synthesis of Saquinavir

The remaining portion of saquinavir, fragment **2**, is usually constructed from quinaldic acid (**5**) and l-asparagine (**6**). An early synthesis of saquinavir completed this portion by beginning with Cbz-protected l-asparagine (**64**) and coupling it to pentafluorophenol using dicyclohexylcarbodiimide (DCC) to provide **65** (Scheme 15).[20] Reaction of pentafluorobenzene ester **65** with **66** gave compound **67** (Scheme 15), which subsequently was coupled to **68** (produced by the activation of quinaldic acid (**5**) using *N*-hydroxysuccinimide (NHS) and DCC, Scheme 16), to produce saquinavir (**1**).

A more convergent approach, which also decreased the number of steps has been developed.[20] In this synthesis, quinaldic acid (**5**) was coupled to l-asparagine via activation with *N*-hydroxysuccinimide to provide **2** in 82–85% yield for the **4** step coupling procedure (Scheme 17). The quinargine thus produced was reacted with **67** and DCC along with a catalytic amount of *N*-hydroxypyridone to afford saquinavir mesylate (**69**) in 81% yield after recrystallization of the mesylate salt.

An alternative procedure for the coupling of decahydroisoquinoline derivative **4** with azidoepoxide **15** in good (75%) yield, which does not require heating has been published.[23] In this scheme, silica gel is added to a chloroform solution of amine **4** and epoxide **15**, and after removal of the solvent under reduced pressure, allowed to stand for 3 days (Scheme 18). Azidodecahydroisoquinoline **50** can be isolated by simply adding the solid to a silica gel column and purifying. This method may have advantages when using more temperature sensitive substrates.

3 Nelfinavir (Viracept®, AG1343)

Nelfinavir mesylate, Viracept®, approved in March, 1997 is another potent inhibitor of the HIV protease enzyme, which contains a hydroxyethylamine isostere. Marketed by Agouron Pharmaceuticals, nelfinavir (**70**, Figure 3) exhibits an ED_{50} value of 14 nm.[24]

As seen in Figure 3, nelfinavir (**70**) can be disconnected into three units. Fragment **4** is the same decahydroisoquinoline contained in saquinavir. The transition state mimic in

nelfinavir, **71**, is a hydroxyethylamine isostere with an *S*-phenyl substituent, which replaces the phenyl group found in the saquinavir isostere. Finally, the isostere is coupled with 3-hydroxy-2-methylbenzoic acid (**72**), or a suitable equivalent.

3.1 Synthesis of the Nelfinavir Isostere

The main challenge in the synthesis of nelfinavir involves construction of the unusual hydroxyethylyamine isostere (**71**). One approach to the nelfinavir isostere utilizes 1,3-dithiane.[25] Reiger's synthesis begins with *N*-Cbz-*S*-phenyl-l-cysteine (**73**), produced by a previously described method.[26] Synthesis of the *N,N*-dimethyl amide proceeded by exposure of **73** to pivaloyl chloride followed by in situ displacement of the mixed anhydride by dimethylamine and afforded amide **74** in 98% yield (Scheme 19). Addition of the anion derived from the treatment of 1,3-dithiane with *n*-BuLi to dimethyl amide **74** followed by reduction with $NaBH_4$ afforded alcohol **75** in 70% isolated yield from a 4.5:1 mixture of diastereomers. Removal of the dithiane group was effected by treatment with $Hg(ClO_4)_2$ $3H_2O$ to give unstable aldehyde **76** which was immediately used in the following reductive amination step. Thus, treatment of **76** with **4**, molecular sieves, and $NaBH_4$ yielded **77** in 68% yield and 83% ee from **75**. Amino alcohol **77** could then be converted to nelfinavir (**70**) by established procedures.[27]

In another approach, a chiral 2-amino-1,3,4-butanetriol was used as a building block in the synthesis of nelfinavir.[28] This synthesis began with readily available 4,4-dimethyl-3,5,6-trioxa-bicyclo[5.1.0]octane (**78**), which underwent asymmetric ring opening using a chiral Ti catalyst to provide amino alcohol **79** in nearly quantitative yield and >97% de (Scheme 20).[29] Amino alcohol **79** was then transformed into protected amino triol benzoic acid salt **80** in 82% yield by the following one pot procedure: conversion to the more thermodynamically stable dioxolane using 2,2-dimethoxypropane (DMP) and MsOH in acetone followed by debenzylation with Pd/C and H_2 in the presence of benzoic acid. Amine **80** was protected as the benzyl carbamate using CbzCl and K_2CO_3. Replacement of the free alcohol by an *S*-phenyl group was accomplished by first forming the mesylate with MsCl and TEA followed by displacement using thiophenol/NaOH/Bu_4NBr which afforded **81**. The acetonide was then removed from **81** by refluxing with HCl in MeOH/H_2O and the resulting primary alcohol was selectively protected as the *p*-nitrobenzyl (PNB) ether using PNBCl and 2-picoline to provide alcohol **82**. Reaction of alcohol 82 with MsCl provided the corresponding mesylate, which was then epoxidized by in situ removal of the PNB protecting group using KOH to afford **83** in 82% yield from **80**, thus completing the isostere synthesis.

There have been many reports of syntheses of unnatural *S*-phenyl cysteine in the literature. Some of the methods described include: opening of a serine derived -lactone intermediate with a thiophenol based nucleophile,[26,30] displacement of a serine derived tosylate by a thiolate anion,[31] opening of an aziridinecarboxylic acid by thiophenol,[32] Michael addition of thiophenol to a chiral nickel complex incorporating an electrophilic alanine-type substituent,[33] and an enzymatic process using cysteine desulfhydrase.[34]

One synthesis of nelfinavir created the isostere via a -lactone ring opening using a thiophenol nucleophile. In the synthesis by Kaldor et al. in 1997, treatment of Cbz protected l-serine (**84**) with PPh_3 and dimethylazidodicarboxylate (DMAD) produced lactone **85**, which was then reacted in situ with the thiolate anion derived from thiophenol and NaH to afford Cbz protected *S*-phenyl cysteine (**73**) in 39% overall yield (Scheme 21).[24] Reaction of **73** with *iso*-butylchloroformate followed by CH_2N_2 generated the diazoketone in 73% yield, which was subsequently treated with HCl to provide chloromethyl ketone 86. Sodium borohydride reduction of ketone **86** produced chloro alcohol **87** in 39% isolated yield from a mixture of diastereomers. Base induced cyclization of alcohol **87** using KOH/EtOH afforded epoxide **83** in 85% yield to complete the synthesis of the isostere portion of nelfinavir.

3.2 Synthesis of Nelfinavir

Construction of nelfinavir then proceeded via coupling of epoxide **83** with decahydroisoquinoline derivative **4** in refluxing ethanol followed by Cbz deprotection with HBr/AcOH to afford **77** in 28% yield from **83** (Scheme 21). Finally, reaction of **77** with 3-hydroxy-2-methylbenzoic acid (**72**) in the presence of DCC and 1-hydroxybenzotriazole (HOBt) provided nelfinavir (**70**) in 59% yield.

A different approach to the synthesis of nelfinavir proceeded through an oxazoline intermediate.[35] Thus, epoxide **78** was opened with (*R*)-methylbenzylamine (**88**) to afford the *trans* amino alcohol in 39% yield, which was subsequently hydrogenated with H_2, Pd/C and AcOH to give amino alcohol acetate salt **89** (Scheme 22). Reaction of **89** with 3-acetoxy-2-methylbenzoyl chloride (**90) gave** the corresponding amido alcohol, which, upon treatment with MsCl, yielded mesylate **91**. Addition of BF_3 OEt_2 to a solution of **91** followed by quenching with acetic anhydride produced oxazoline **92** in 71% yield. Heating a solution of **92**, K_2CO_3 and amine **4** in methanol at 50 °C afforded **93** in 65% yield from **89**. Oxazoline **93** was then converted to nelfinavir (**70**) in 81% yield by reaction with thiophenol using $KHCO_3$ as base and methyl *iso*-butylketone (MIBK) as solvent. It is worth noting that the reaction conditions employed were critical. The use of ethylene glycol as solvent with no base for example, led to product formation in a ratio of 18:82 (nelfinavir–regioisomer) while the conditions stated above led to a 92:8 product distribution.

A similar approach to nelfinavir that also goes through an oxazoline intermediate was published by Zook et al. in 2000.[36] Beginning with epoxide **94**, catalytic asymmetric ring opening with azidotrimethylsilane produced the corresponding azide in 96% yield and >99% ee.[37] The corresponding product was subsequently deprotected, hydrogenated and converted to the corresponding tosylate salt (**95**) (Scheme 23). Treatment of **95** with commercially available 3-acetoxy-2-methylbenzoyl chloride and triethylamine (TEA) gave the corresponding amide, which was then reacted with MsCl to afford mesylate **96**. Without any purification, the freshly prepared mesylate was reacted with excess acetic anhydride and concentrated H_2SO_4 to provide oxazoline **92**. The oxazoline thus produced was coupled with amine **4** using MeOH and K_2CO_3 to afford **93** in 72% yield from tosylate salt **95**. Finally, reaction of **93** with thiophenol and $KHCO_3$ in MIBK produced nelfinavir (**70**) in 82% yield to complete the synthesis.

Moiety **72** and the corresponding acid chloride are both commercially available, however 3-hydroxy-2-methylbenzoic acid can also be prepared as in Scheme 24. Treatment of commercially available 3-amino-2-methylbenzoic acid (**97**) with concentrated H_2SO_4 and sodium nitrite afforded **72** in 52% yield.[24]

4 Amprenavir (Agenerase®, VX-478, 141W94)

One of the more recently approved HIV protease inhibitors is amprenavir, discovered by scientists at Vertex Pharmaceuticals and currently marketed as Agenerase® by Glaxo Wellcome. This molecule resulted from the desire to find smaller weight protease inhibitors, which it was hoped, would enhance the oral bioavailability while still maintaining or increasing potency. Amprenavir, approved in April 1999 by the FDA, has a K_i value of 0.6 nM against HIV-1 and, with a molecular weight of 505.64, is the smallest of the 6 currently approved HIV protease inhibitors.[38]

As can be seen in Figure 4, amprenavir (**98**) can be disconnected into 3 fragments of which **3** is the common benzyl substituted amino epoxide which can be used to form the central hydroxyethylamine isostere. Moiety **99** is commercially available *(S)*-3-hydroxytetrahydrofuran, which can be activated to form the P_1 carbamate ligand. The remaining portion of amprenavir (**100**) can be synthesized from *iso*-butylamine (**101**) and an activated benzenesulfonyl derivative such as *p*-nitrobenzenesulfonyl chloride (**102**).

4.1 Synthesis of the Amprenavir Isostere

Ghosh and Fidanze have developed a flexible synthesis which allows access to the hydroxyethylamine isostere found in amprenavir, saquinavir and nelfinavir, as well as the hydroxyethylene isostere, which occurs in ritonavir, lopinavir, and indinavir.[39] Their approach utilizes asymmetric *syn*- and *anti*-aldol chemistry using *N*-tosyl-*cis*-aminoindanol as a chiral auxiliary. In the synthesis leading to amprenavir, *N*-tosyl-*cis*-aminoindanol (**103**) is coupled to 3-phenylpropionic acid using 4-dimethyl aminopyridine (DMAP) and DCC to afford ester **104** in 85% yield (Scheme 25). Aldol reaction between the titanium enolate of **104** (generated using $TiCl_4$ and Hünig's base) and benzyloxy-acetaldehyde provided *syn*-aldol product **105** as a single isomer in 97% yield. Removal of the chiral auxiliary by treatment with hydrogen peroxide and LiOH occurred in 82% yield. Exposure of the resulting acid to diphenylphosphorylazide (DPPA) and TEA initiated a Curtius rearrangement, which resulted in formation of oxazolidinone **106** in 75% yield. Hydrolysis of 106 by KOH followed by protection of the free amine as the *t*-butyloxycarbonyl, (Boc) derivative produced alcohol **107** in 87% yield from oxazolidinone **106**. Removal of the *O*-benzyl protecting group by hydrogenation over Pearlman's catalyst followed by reaction with PPh_3 and DEAD afforded the desired amino epoxide (**108**) in 61% yield from **107**.

A remarkably straightforward synthesis of the amprenavir isostere is outlined in Scheme 26 and involves the diastereoselective addition of an amino carbanion to protected phenylalanal.[40] Beginning with *N,N*-dibenzyl protected l-phenylalanal (**51**), reaction with the anion derived from lithium diisopropylamine and *N*-methyl-*N*-nitrosoisobutylamine gave **109** as a 4:1 mixture of *syn*:*anti* diastereomers in 83% combined yield. Removal of the benzyl protecting groups with H_2 and Pearlman's catalyst followed by reprotection with Boc_2O

proceeded in 89% yield. Finally, treatment of the nitroso derivative with H_2 and Raney nickel afforded *iso*-butyl amine **110** in 64% yield which could be further elaborated to furnish amprenavir (**98**).

Another approach to the hydroxyethylamine isostere was developed by Beaulieu and co-workers.[41] The synthesis begins with l-phenylalanine (**45**). Reduction of the acid to the alcohol took place using $NaBH_4$ and H_2SO_4, followed by protection as the *N,N*-dibenzyl derivative using BnBr and K_2CO_3, afforded alcohol **111** (Scheme 27). Oxidation using sulfur trioxide provided dibenzyl protected l-phenylalanal (**51**) in 99% yield. Reaction of this aldehyde with bromochlororomethane and Li metal (15 equiv) at – 65 °C gave the analogous epoxide, which was immediately treated with 6 N HCl to afford hydrochloride salt **112** in 45% yield from phenylalanol. Removal of the benzyl protecting groups was accomplished by hydrogenating over Pearlman's catalyst to afford **113** in 97% yield. To complete the isostere synthesis, **113** was reprotected with Boc_2O and subsequently cyclized with methanolic KOH to provide 108 in 96% yield.

4.2 Synthesis of Amprenavir

There have been very few total syntheses of amprenavir in the literature. Corey and Zhang have published one such synthesis which uses a chiral quaternary ammonium salt to promote a diastereoselective nitroaldol reaction.[42] Reaction of dibenzyl protected l-phenylalanal (**51**) with 10 mol% of chiral ammonium salt **114**, nitromethane, and excess KF in THF at −10 °C afforded corresponding nitro alcohol **115** in 86% yield as a 17:1 ratio of diastereomers in favor of **115** (Scheme 28). Treatment of **115** with $NiCl_2$ and a large excess of $NaBH_4$ provided amino alcohol **116** in 85% yield. Formation of the corresponding imine by reaction of amine 116 with *iso*-butyraldehyde followed by reduction using $NaBH_4$ produced amino alcohol **117** in 82% yield. Reaction of **117** with *p*-nitrobenzenesulfonyl chloride (**102**) gave the corresponding sulfonamide in 94% yield, which was deprotected with H_2 and Pearlman's catalyst to afford **118**. Finally, coupling of amine **118** with the *N*-oxysuccinimidyl carbonate of (*S*)-3-hydroxytetrahydrofuran produced amprenavir (**98**) in 50% overall yield from **51**.

Another total synthesis was recently published by Kim et al., which is especially noteworthy because it allows easy access to protease inhibitors that use hydroxyethylamine isosteres not derived from naturally occurring amino acids.[43] The synthesis begins with D-tartaric acid (**119**) which is first esterified with $SOCl_2$ and MeOH followed by protection of the diol as the acetonide with 2,2-dimethoxypropane (DMP) and *p*-TsOH and subsequent reduction to diol **120** using $NaBH_4$ in ~85% overall yield (Scheme 29). Transformation of diol **120** to the corresponding dichloride (**121**) was completed in 50% yield by treatment with MsCl, LiCl and TEA. Conversion to the cyclic sulfate was accomplished by treating **121** $SOCl_2$ followed by oxidation using $RuCl_3$ with $3H_2O$ and sodium periodate to afford **122** in 95% yield. The Boc-protected nitrogen was introduced into the molecule by opening the cyclic sulfate with potassium phthalimide (KPhth) in DMF, removal of the phthayl group by treatment with hydrazine followed by HCl, and reprotection as the *t*-butyl carbamate using Boc_2O, which afforded **123** in 75% yield from cyclic sulfate **122**. Protection of the free alcohol as the *t*-butyldimethylsilyl (TBS) ether was accomplished by reaction with TBSCl.

Next the aziridine was formed by treatment with NaH to furnish **124** in near quantitative yield, which completed the carbon skeleton of the isostere portion of amprenavir. Introduction of the benzyl side chain of the amprenavir isostere was accomplished by treating **124** with phenyllithium and CuBr DMS, which selectively opened the aziridine to afford **125** in 75% yield. The epoxide was then formed by deprotecting **125** with tetrabutylammonium fluoride (TBAF), and subsequent treatment with KOH in methanol. Opening the epoxide with *iso*-butyl amine proceeded in 90% yield. The corresponding alcohol was subsequently reacted with *p*-nitrobenzenesulfonyl chloride (**102**) to afford **126** in 88% yield. Removal of the Boc group with HCl gave the free amine, which was then reacted with the active carbonate of (*S*)-3-hydroxytetrahydrofuran to provide **127** in 85% yield. Lastly, reduction of the nitro group in **127** was accomplished by treatment with $SnCl_2$ $2H_2O$ to afford amprenavir (**98**) in 90% yield.

5 Indinavir (Crixivan®, I-735,524, MK-639)

Crixivan® (**128**, Figure 5) is the trade name for indinavir sulfate. The FDA approved indinavir sulfate for the treatment of HIV and AIDS in March of 1996.[44] This inhibitor exhibits an IC_{50} value of 0.56 nM ± 0.2 nM and a CIC_{95} value of 25–100 nM.

The structure of this inhibitor can be disconnected into three fragments: the piperazine moiety, the Phe-Gly hydroxyethylene isostere and the (−)-*cis*-(1*S*,2*R*)-1-aminoindan-2-ol [(−)-CAI] moiety, as shown in Figure 6. The first total synthesis of indinavir was published by Merck Research Laboratories in 1994.[45] They used a convergent approach for the construction of indinavir where the piperazine moiety was derived from (*S*)-2-piperazinecarboxylic acid (**129**),[46] the hydroxyethylene isostere was derived from commercially available, optically active (*S*)-(+)-dihydro-5-(hydroxymethyl)-2(3*H*)-furanone (**130**) and the (−)-*cis*-(1*S*,2*R*)-1-aminoindan-2-ol moiety was derived from indene (**131**).[47]

5.1 Synthesis of the Indinavir 2-Piperazine Fragment

The synthetic route began with (*S*)-2-piperazinecarboxylic acid bis[(*S*)-(+)-camphorsulfonic acid] salt (**132**, Scheme 30). This starting material can be produced via the method of Felder et al., which entails the hydrogenation of pyrazinecarboxylic acid followed by resolution through crystallization with (*S*)-(+)-camphorsulfonic acid.[46] The synthetic route towards indinavir continued with sequential protection of the amine functionalities as *t*-butylcarbamate and benzyl carbamate in 96% yield followed by amidation with *t*-butylamine. Removal of the Cbz protecting group was accomplished using hydrogenation over 10% Pd/C in methanol to afford intermediate **133** in 96% yield.

This piperazine fragment can also be produced by amidation of 2-pyrazinecarboxylic acid (**134**) with oxalyl chloride and *t*-butylamine followed by hydrogenation using Pearlman's catalyst and (*S*)-camphorsulfonic acid [(*S*)-CSA] to afforded the corresponding optically active salt (Scheme 31).[48] Selective protection of N_4 of the resulting product using Boc_2O and TEA afforded optically active *t*-butyl amide **133** in 26% overall yield.

A modified preparation of the piperazine fragment of indinavir was developed by Rossen et al.[49] It proceeds from the *t*-butylamide derived from 2-pyrazinecarboxylic acid (**135**,

Scheme 32). Partial hydrogenation of the pyrazine ring followed by sequential protection of the resulting amine moieties produced intermediate **136** in 62% overall yield. Catalytic hydrogenation of **136** with 2% [(*R*)-BINAP(COD)Rh]TfO in methanol afforded **138** in 96% yield with 99% ee. Removal of the Cbz group was accomplished by hydrogenation over Pd/C in methanol to afford the desired piperazine derivative (**133**) in >99% ee.

5.2 Synthesis of the Indinavir Isostere

Chakraborty and Gangakhedkar have devised a synthesis of the Phe-Gly hydroxyethylene isostere starting from d-glucose (**139**).[50] As shown in Scheme 33, d-glucose (**139**) was converted into protected derivative **140** using known carbohydrate transformations.[51] Tosylation of the primary alcohol was followed by displacement using sodium azide and afforded azidoalcohol **141**. Benzyl protection of the remaining alcohol followed by thioacetal protection of the ring-open form of the pyranoside afforded **142** in 80% yield over two steps. Acetate protection of the resulting alcohol followed by deprotection of the dithioacetal, oxidation of the resulting aldehyde, and esterification of the acid afforded ester **143** in 56% yield (4 steps). Deprotection and activation of the resulting alcohol with triphenyl phosphine led to aziridine formation affording the desired isomer (**144**) in 70% isolated yield after Boc protection. Regioselective opening of the aziridine was accomplished using phenyl Grignard in the presence of CuBr DMS. This produced the desired Phe-Gly hydroxyethylene isostere (**145**) in 70% yield.

Maligres et al. published an efficient synthesis of epoxide **146** which contains the epoxide equivalent of the indinavir isostere.[52] The key steps of this synthesis are the stereoselective allylation of **147** and the stereoselective epoxidation of the resulting olefin. Thus, as shown in Scheme 34, aminoindanol derivative **147** was treated with LiHMDS and allyl bromide to afford a 96:4 ratio of the corresponding olefins in 94% yield (major diastereomer shown, **148**). The resulting major product was converted into iodohydrin **149** via treatment with *N*-chlorosuccinimide (NCS) in a mixture of *i*-propylacetate and aqueous sodium bicarbonate followed by an aqueous solution of sodium iodide. These conditions afforded primary iodohydrin **149** in 92% yield (94% de). Addition of a 25% solution of sodium methoxide to iodohydrin **149** in *i*-propylacetate afforded epoxide **146** in near quantitative yield. This resulted in formation of the key epoxide in an overall yield of 86% from **147**.[53]

5.3 Synthesis of Indinavir

Rossen and co-workers' total synthesis of indinavir at Merck began by improving the efficiency of the construction of the piperazine fragment as shown in Scheme 35.[54] Thus, condenstaion of *N*-Boc-ethylenediamine (**150**), dichloroacetaldehyde (**151**), *t*-butylisocyanideformic acid followed by treatment with triethylamine led to the formation of intermediate **152** in quantitative yield. Deprotonation with *t*-BuOK led to cyclization (60% yield), which was followed by catalytic hydrogenation using Rh-BINAP (quantitative yield, 97% ee). The formyl protecting group was cleanly removed using hydrazine to afford the desired piperazine fragment (**133**) in 91% yield without racemization of the chiral center (98% ee).

The synthesis of indinavir continued by coupling piperazine **133** with the triflate derivative of furanone **130**. This triflate derivative (**154**) was constructed via alkylation of the corresponding protected lactone (Scheme 36). This alkylation was accomplished by protection of (*S*)-(+)-dihydro-5-(hydroxymethyl)-2(3*H*)-furanone (**130**) with *t*-butyldimethylsilyl chloride (TBSCl) followed by treatment with *n*-BuLi, diisopropylamine, and benzyl bromide to yield alkylated lactone 153. Deprotection of the silyl group with HF in acetonitrile followed by conversion of the resulting alcohol to a triflate yielded derivative 154 in 66% yield over four steps.

Having two of the three fragments for indinavir completed, Merck Laboratories turned to the synthesis of the third fragment, (−)-*cis*-(1*S*,2*R*)-1-aminoindan-2-ol. Merck's synthesis of (−)-*cis*-(1*S*,2*R*)-1-aminoindan-2-ol begins with the conversion of indene (**131**) to optically active indene oxide (156), as shown in Scheme 37.[47,55] This was accomplished using Jacobsen's epoxidation catalyst, *S*,*S*-(salen)Mn(III)Cl (**155**), 4-(3-phenylpropyl)pyridine *N*-oxide (P_3NO) and aqueous sodium hypochlorite and afforded indene oxide in 89% yield with an enantiomeric excess of 88%. Indene oxide was then converted into methyl oxazoline **157** by treatment with oleum in acetonitrile. Hydrolysis of the oxazoline followed by crystallization with l-tartaric acid yielded (−)-*cis*-(1*S*,2*R*)-1-aminoindan-2-ol (**158**) in 50% overall yield with greater then 99% enantiomeric excess.

Completion of the synthesis of indinavir was accomplished by the coupling of triflate derivative **154** with piperazine **133** using diisoproplylethylamine in *iso*-propanol (Scheme 38). This afforded the corresponding coupled product in 83% yield. Hydrolysis of the lactone using lithium hydroxide yielded the hydroxyethylene isostere, which was protected as a *t*-butyldimethylsilyl ether in 96% yield over two steps. Coupling of the resulting acid with (−)-*cis*-(1*S*,2*R*)-1-aminoindan-2-ol (**158**) using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) resulted in intermediate **159**. The completion of the synthesis of indinavir was accomplished by removal of the silyl and Boc protecting groups using hydrochloric acid and finally, coupling of the piperazine with 3-picolyl chloride. The synthesis provided indinavir in ten steps with an overall yield of 35%. A separate synthetic route to indinavir was devised using coupling of epoxide **146** with piperazine fragment **133**, as shown in Figure 7. This synthesis is different from the previous in that it creates the isostere hydroxy group via opening of an epoxide.

This route begins with the synthesis of the (−)-*cis*-(1*S*,2*R*)-1-aminoindan-2-ol fragment. This was achieved by *N*-alkylation of (−)-*cis*-(1*S*,2*R*)-1-aminoindan-2-ol (158) with 3-phenylpropionyl chloride (**161**) followed by protection of the resulting amidoalcohol as an acetonide (Scheme 39).[56] The resulting amide derivative (**162**) was then functionalized at the α-carbon using LiHMDS and commercially available (*S*)-(+)-glycidyl tosylate (**163**). This led to coupled product **146** in 72% yield as a 98:2 ratio of epimers at the α-carbon (major diastereomer is shown). Completion of the synthesis of indinavir was accomplished by coupling of epoxide **146** with piperazine fragment **133**, synthesized as shown in Scheme 32. Coupling of the two fragments along with concomitant deprotection of the acetonide and Boc moieties with HCl afforded the corresponding diol. This intermediate was then coupled with 3-picolyl chloride to afford indinavir in 71% yield (from **146**).

A solid phase synthesis of indinavir was developed by Cheng et al. and it began with linking *N*-Boc-(−)-*cis*-(1*S*,2*R*)-1-aminoindan-2-ol to the Rapp TentaGel S COOH resin via an ester linkage (Scheme 40).[57] This coupling was accomplished using EDC and dimethylaminopyridine (DMAP) in a mixture of dimethylformamide and dichloromethane to yield linked *N*-Boc-(−)-*cis*-(1*S*,2*R*)-1-aminoindan-2-ol **164**. Removal of the Boc protecting group with trifluoracetic acid (TFA) followed by coupling with **165**[45] under standard conditions (EDC/HOBt) afforded intermediate **166**. Boc deprotection (TFA) followed by reductive amination yielded protected indinavir. The silyl group was removed with hydrogen fluoride in pyridine and indinavir was cleaved from the resin using a 9:1 mixture of methanol–TEA at 50 °C. This synthesis provided the target molecule in 71% yield with an optical purity of >95%.

6. Ritonavir (Norvir®, ABT-538)

Norvir® (**167,** Figure 8) is the trade name for ritonavir, an FDA approved (March, 1996) HIV protease inhibitor from Abbott Laboratories. This inhibitor exhibits an EC_{50} value of 0.022–0.13 μM versus HIV-1 and an EC_{50} value of 0.16 μM versus HIV-2.[58]

6.1 Synthesis of the Ritonavir Isostere

This molecule was synthesized at Abbott Laboratories by Kempf et al.[59] The route began with the construction of the Phe-Phe hydroxyethylene isostere moiety. As shown in Figure 8, the isostere can be derived from (*S*,*S*,*S*)-diaminoalcohol **168**. This hydroxyethylene isostere has been prepared via several different routes over the years. Many of the methods used for its construction proceed using an alkylation of lactone **169** as a means of introducing the third stereocenter into the isostere.

Evans et al. published an early synthesis of this type of lactone starting from *N*-Boc-phenylalanine, which they converted into *N*-Boc phenylalanal (**33**, Scheme 41).[60] This aldehyde was subjected to Corey–Chaykovsky epoxidation, which afforded epoxide derivative **170** as a mixture (ca. 1:1) of diastereomers. The epoxide moiety was then opened using the anion of diethylmalonate, and after in situ lactonization and chromatography, the corresponding lactone was isolated in 32% yield from **170**. The α-carbon of the lactone was then alkylated using NaOEt and benzyl bromide. The resulting compound was treated with base, acid and heated to afford a mixture of epimers of the Phe-Phe isostere of ritonavir in 78% yield.

DeCamp et al. completed the synthesis of lactone **169** using addition of a homoenolate to Boc-protected phenylalanal (**33**).[61] Thus, as shown in Scheme 42, addition of the appropriate titanium homoenolate to *N*-Boc phenylalanal (**33**) provided the corresponding alcohol in a 16:1 ratio of diastereomers (major isomer shown, **173**). Refluxing the alcohol with acetic acid in toluene afforded lactone **169** containing two of the stereocenters for the Phe-Phe isostere of ritonavir.

A synthesis of an unsaturated version of lactone **169** was accomplished in 1991 by Harding et al.[62] As shown in Scheme 43, this synthetic route began with compound **174** and proceeded via stereoselective addition of 2-(trimethylsilyloxy)furan (**175**) in the presence of

BF_3 OEt_2. This afforded the corresponding Cbz-protected lactone (**176**) in 70% yield and 74% diastereomeric excess.

Also in 1991, Chu et al. devised a synthesis of lactone **169** starting from D-mannose (**177**).[63] Protection followed by elimination and isomerization of the resulting olefin afforded dihydrofuran derivative **179** (Scheme 44). Hydrogenation and deprotection of the acetonide moiety were followed by formation of an epoxide via elimination of the primary tosylate. Phenyl cuprate was used to open the epoxide and afforded alcohol **181**. Inversion of the resulting alcohol with diphenylphosphoryl azide afforded azide **182** in 92% yield. Lactonization with *m*CPBA followed by hydrogenation of the azide and Boc protection of the resulting amine led to lactone **169**. Chu et al. proceeded to alkylate lactone **169** using LiHMDS and benzyl iodide followed by hydrolysis using trimethyl aluminum and benzyl amine to yield isostere **183**. However, this isostere contains an incorrect stereocenter for incorporation into ritonavir.

Ghosh and co-workers published an improved alkylation procedure in 1993.[64] This proceeded from common lactone **169**, as shown in Scheme 45. Thus, alkylation using LiHMDS and benzyl iodide provided lactone **184**. This was followed by isomerization of the newly created stereocenter using a sequence of: (i) conversion to the corresponding phenyl selenide, (ii) elemination of the selenide using *m*CPBA and (iii) stereoselective hydrogenation of the resulting olefin. This sequence yielded the correct isomer of the alkylated lactone in a combined yield of 71% over the four steps. Ghosh et al. completed their synthesis of the isostere by hydrolyzing the lactone and using a Curtius rearrangement to convert the resulting carboxylic acid moiety to an amide.

Yet another synthesis of lactone **169** was reported in 1992 by Dreyer et al. (Scheme 46).[65] Grignard addition to *N*-Boc phenylalanal (**33**) provided unsaturated alcohol 186 in 78% yield as a mixture of isomers. Acetate protection of the alcohol was followed by permanganate oxidation of the olefin, deprotection of the acetate group and lactonization to afford lactone **169** in 50% yield after chromatography.

Baker and Pratt published a synthesis of the hydroxyethylene isostere of ritonavir starting form alkylated lactone **187**.[66] As shown in Scheme 47, kinetic protonation of lactone **187** using LDA and dimethylmalonate at −78 °C afforded a stereochemically enriched mixture of lactones(9.5:1 for the isomer shown, **185**). Hydrolysis using NaOH followed by silyl protection of the resulting alcohol afforded the ritonavir hydroxyethylene isostere (**188**) containing the correct stereochemistry at all three chiral centers.

Stereoselective reduction of thiazole derivative **189** (Scheme 48) allowed Dondoni and co-workers access to lactone **169**.[67] Thus, treatment of **189**, made from 2-(trimethylsilyl)thiazole addition to activated phenylalanine,[68] with $NaBH_4$ afforded the corresponding alcohol (**190**) in 92% yield (>95% *de*). After silyl protection of the alcohol, a three step procedure was used to convert the thiazole to an aldehyde. The resulting aldehyde (**191**) was subjected to a Wittig reaction to yield the corresponding unsaturated ester (**192**) in 98% yield. Reduction of the double bond was followed by deprotection and lactonization to give **169** in 76% yield over two steps.

Ghosh and co-workers contributed to this body of work again in 1998 with their *anti*-aldol approach to the isostere[39] and in 1999 with their dihydroxylation approach.[69] The *anti*-aldol approach produced aldol **194** (Scheme 49). The chiral auxiliary (*N*-tosyl-*cis*-aminoindanol, **103**) of aldol **194** was hydrolyzed followed by conversion of the resulting acid to an amine via a Curtius rearrangement and Boc protection to afford allylic alcohol **195**. Ozonolysis of the olefin was followed by Horner– Emmons–Wittig reaction of the resulting aldehyde, hydrogenation of the double bond and acidic lactonization to provide **169**. Alkylation and hydrolysis in the presence of benzylamine completed the isostere synthesis.

As shown in Scheme 50, Ghosh's dihydroxylation approach proceeded by treatment of unsaturated ester **197** with AD-mix-β and methanesulfonamide to afford lactone **198** in 87% yield.[69] Inversion of the hydroxy stereochemistry was achieved by conversion to the mesylate and substitution using sodium azide. Upon reduction of the azide and protection using Boc anhydride, the lactone was alkylated using LiHMDS and benzyl iodide to afford **200**.

Finally, as shown in Scheme 51, inversion of the lactone oxygen was accomplished by, (after hydrolysis and several protection/deprotection steps) conversion of **201** to the oxazolidinone using SO_2Cl_2 (73% yield). Hydrolysis of the oxazolidinone and protection of the resulting amines with Boc anhydride yielded the hydroxyethylene isostere (**202**) in 52% yield (2 steps).

A different approach to the isostere was taken by Hanessian et al. in which alkylation of lactone **169** was not necessary.[70] Thus, as shown in Scheme 52, addition of (2-bromomethyl)acrylate to protected phenylalanal **203** in the presence of zinc dust afforded a 90% yield of olefin **204**. Acidic lactonization was followed by phenyl cuprate addition to give lactone **206** in 86% diastereomeric excess. Isomerization of the hydroxy stereocenter after a deprotection/protection sequence yielded lactone **184** containing one incorrect stereocenter for the ritonavir isostere.

Another synthesis of the Phe-Phe hydroxyethylene isostere that does not proceed through lactone **169** was published by Kempf and co-workers.[71] They originally constructed the hydroxyethylene isostere for ritonavir starting from Cbz-phenylalanol (**208**, Scheme 53). Vanadium-mediated coupling of two molecules of the corresponding aldehyde of **208** proceeded to give an 8:1:1 mixture of diols in favor of **209**.

Kempf et al. continued by dehydration of diol **209**.[72] Thus, treatment of **209** with α-acetoxyisobutyryl bromide yielded the corresponding bromoacetate (**210**, Scheme 54). Reductive debromination followed by hydrolysis of the protecting groups afforded isostere **211** in 81% yield (3 steps).

D'Aniello et al. published another route to the hydroxyethylene isostere of ritonavir.[73] This route, shown in Scheme 55, began with the addition of 2-(chloromethyl)-3-(trimethylsilyl)-1-propene to *N*-Boc phenylalanal (**33**). This afforded homoallylic alcohol **212** in 84% yield and 90% diastereomeric excess. After acetonide protection, halogen exchange and treatment with phenyl cuprate afforded a 76% yield of compound **214**.

Hydroboration of the olefin of **214** resulted in a 58% yield (62% de) of alcohol **215**. Oxidation to the acid followed by amidation and acidic deporotection of the acetonide yielded isostere **183**. This isostere, however, contains an incorrect stereocenter for ritonavir.

Benedetti et al. elaborated epoxide **216**,[74] shown in Scheme 56, into the hydroxyethylene isostere of ritonavir.[75] This was accomplished starting with reduction of the epoxide with Red-Al in THF (60% yield). Mesylation of the diol resulted in spontaneous oxazolidinone formation and the remaining mesylate was displaced using sodium azide to afford **218**. Protection of the carbamate nitrogen with Boc_2O followed by hydrolysis of the oxazolidinone and hydrogenation of the azide afforded isostere **219** in 67% yield over three steps.

The actual isostere synthesis reported by Abbott Laboratories is based on the reduction of an enaminone.[76] Thus phenylalanine (**45**) was treated with benzyl chloride in the presence of K_2CO_3 to yield the corresponding protected benzyl ester (Scheme 57) in 94% yield. An acetonitrile anion was added to the benzyl ester to afford **220** in a yield of at least 78% after recrystallization (>98% ee). Benzyl Grignard addition to the resulting nitrile afforded key enaminone **221** in greater than 99.5% enantiomeric excess and 94% yield after recrystallization. Selective reduction of the enaminone was accomplished by treatment with a complex of $NaBH_4$ and methanesulfonic acid (MsOH) followed by a second reduction step with $NaBH_4$ in the presence of triethanolamine. This provided greater than 98% conversion of **221** to **222** with a diastereomeric excess of 84%. Compound **222** can easily be converted into the desired diamine (**211**) via hydrogenation.

6.2 Synthesis of Ritonavir

With the isostere (**211**) in hand, Abbott's synthesis turned to construction of the remaining fragments and coupling to form ritonavir.[59] The thiazolyl carbamate fragment of ritonavir was elaborated as shown in Scheme 58. Thus, condensation of thioformamide (**223**) and ethyl-2-chloro-2-formylacetate (**224**) followed by reduction of the resulting ester afforded 5-(hydroxymethyl)thiazole (**225**) in 45% yield (2 steps). Conversion of this thiazole to the corresponding (*p*-nitrophenyl)carbonate was followed by coupling with diamine **211**. This resulted in carbamate **227** in 16% isolated yield.

Elaboration of the remaining fragment of ritonavir was accomplished by coupling valine methyl ester (**228**) with *N*- methyl-*N*-[(2-isopropyl-4-thiazolyl)-methyl]amine. Thus, as shown in Scheme 59, valine methyl ester (**228**) was activated as a (*p*-nitrophenyl)carbamate.

N-methyl-*N*-[(2-isopropyl-4-thiazolyl)-methyl]amine (**233**) was constructed through conversion of *iso*-butyramide (**230**) to 2-methylpropane thioamide (**231**) via treatment with P_4S_{10} (Scheme 60). This was followed by condensation with 1,3-dichloroacetone and methylamine to afford *N*-methyl-*N*-[(2-isopropyl-4-thiazolyl)-methyl]amine (**233**) in 55% yield over two steps.

Coupling of *N*-methyl-*N*-[(2-isopropyl-4-thiazolyl)-methyl]amine (**233**) and valine derivative **229** was accomplished through treatment with TEA and DMAP. This resulted in the final fragment (**234**) of ritonavir in 54% yield.

Coupling of fragments **227** and **234** proceeded under standard conditions (EDC/HOBt) to afford ritonavir in 74% yield.

7 Lopinavir (Aluviran®, ABT-378, Component of Kaletra®)

Lopinavir (**235**, Figure 9) is an FDA approved (September, 2000) HIV protease inhibitor from Abbott Laboratories. This therapeutic is contained in a protease inhibitor formulation (Kaletra®) that includes ritonavir.[77] Ritonavir is known to inhibit cytochrome P-450 3A, the enzyme responsible for metabolism of lopinavir,[78] therefore the combination allows for increased plasma levels of lopinavir. Both ritonavir and lopinavir contain the same Phe-Phe hydroxyethylene isostere subunit. The retrosynthetic disconnections for lopinavir can be seen in Figure 9. This shows that construction of lopinavir can be accomplished via coupling of isostere fragment **168** with acids **236** and **237**.

7.1 Synthesis of the Lopinavir Cyclic Urea Fragment

The synthesis of lopinavir from Abbott Laboratories began by preparation of acid **237**.[79] As shown in Scheme 63, valine (**238**) was coupled with phenylchloroformate to afford carbamate derivative **239** in 92% yield. This carbamate was treated with 3-chloropropylamine and NaOH followed by *t*-BuOK to afford the target acid (**237**) in 77% yield.

7.2 Synthesis of Lopinavir

Acid **237** was then transformed into the corresponding acid chloride for coupling with the hydroxyethylene isostere (Scheme 64). This transformation was accomplished using thionyl chloride in THF allowing for isolation of the acid chloride (**240**) in quantitative yield. Coupling of **240** with isostere **241**[80] was accomplished using three equivalents of imidazole in ethyl acetate and dimethylformamide. This coupling proceeded in quantitative yield along with the subsequent debenzylation using transfer hydrogenation conditions. Crystallization of crude **243** with (*S*)-2-pyrrolidone-5-carboxylic acid (l-pyroglutamic acid, **242**) afforded an 80% yield of pure **243**.

Acid **236**[81] was then converted into acid chloride **244** for use in coupling with fragment **243**. This was accomplished, as shown in Scheme 65, by treatment with SO_2Cl_2 in ethyl acetate and dimethylformamide. This acid chloride was coupled with fragment **243** in a buffered mixture of ethyl acetate and water. This afforded lopinavir (**235**) in 89% yield and greater than 99% purity after recrystallization. This reaction sequence allowed for the production of lopinavir in 58% overall yield form the isostere fragment and greater than 99% diastereomeric excess.

8 Conclusion

This review reports the synthesis of currently approved HIV protease inhibitor drugs. All of these inhibitors contain multiple chiral centers, therefore the synthesis of hundreds of thousands of kilograms of inhibitor drugs in optically pure form is a tribute to asymmetric synthesis. While the current therapies have helped in the fight against HIV and AIDS, the epidemic is still raging. Approximately 95% of people with HIV live in developing

countries. The current therapies are very expensive and possess other limitations as well. These include: (i) low oral bioavailability, (ii) necessity of higher therapeutic doses, (iii) inability to cross the blood-brain barrier, and most concerning, (iv) the development of viral resistance to drugs. Thus, the search for less expensive, more effective, new protease inhibitors that are not cross resistant to current therapies is of critical importance. There are currently three experimental protease inhibitors undergoing clinical evaluations: tipranavir (Boehringer Ingelheim), atazanavir (Bristol-Myers Squibb) and mozenavir (Triangle Pharmaceuticals). These, along with other therapeutics currently in development will add to the arsenal against the current HIV epidemic. This timely application of powerful organic synthetic methodologies to meet today's challenges may serve as an inspiration to deal with other complex human ailments. We hope that this review will stimulate further research and inspiration in the development of protease inhibitors and other peptidomimetic drugs.

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Biographical Sketches

Arun K. Ghosh was born in India in 1958. He obtained his Ph.D. from the University of Pittsburgh with Professor Alan P. Kozikowski (1985). After his postdoctoral studies with Professor E. J. Corey at Harvard University (1985–1988), he joined Merck Research Laboratories (West Point) as a Senior Research Chemist. In 1994, he moved to the University of Illinois at Chicago where he is currently Professor of Chemistry. His current research interests include: development of asymmetric synthetic methodologies; asymmetric catalysis; total synthesis of biologically important natural products; design and synthesis of molecular probes for biological systems; peptidomimetic design and molecular modeling.

Geoffrey Bilcer was born in 1973 and raised near Chicago, Illinois. He received his B.A. in chemistry from Northwestern University in Evanston, Illinois in 1995. After working in industry for two years, he began his graduate studies at the University of Illinois at Chicago. Geoff is working towards his Ph.D. under Professor Arun Ghosh, focusing on the areas of bioactive natural product synthesis and the design and synthesis of various peptidomimetic protease inhibitors. He was awarded a National Science Foundation fellowship for the 2000–2001 academic year. Geoff anticipates completion of his Ph.D. studies in early 2002.

Gary Schiltz was born in Bismarck, N.D. in 1974 and grew up near Chicago, Illinois. He received a B.S. in chemistry from the University of Illinois at Urbana-Champaign in 1997. In 1999 he enrolled at the University of Illinois at Chicago and subsequently joined Professor Ghosh's research group. He is currently working towards his Ph.D. with his research focusing on design and synthesis of selective aspartyl protease inhibitors.

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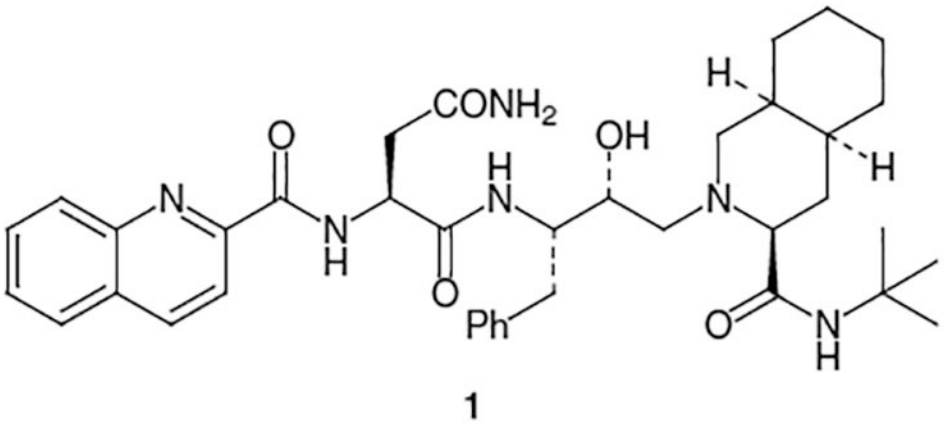

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Figure 1.
Structure of Saquinavir (Invirase®, Fortovase®, Ro 31–8959)

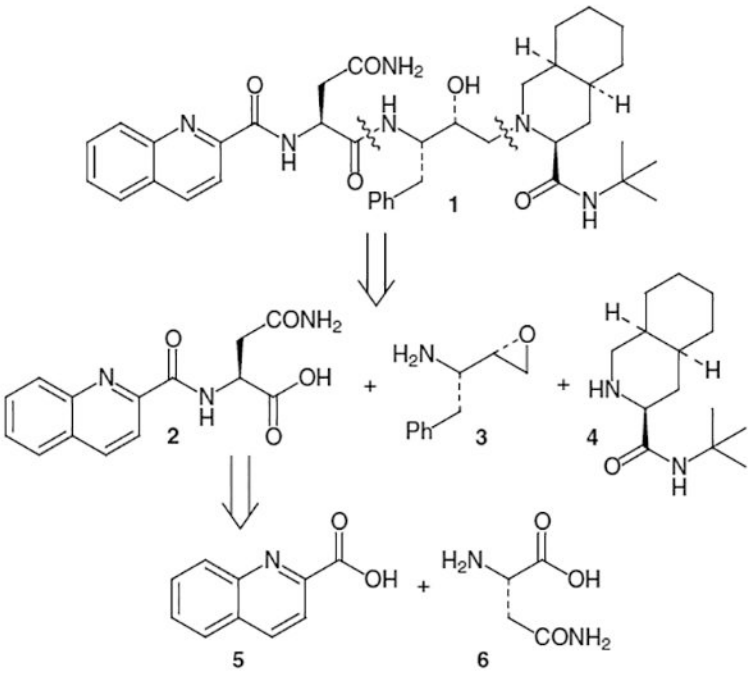


Figure 2.
Retrosynthesis of Saquinavir

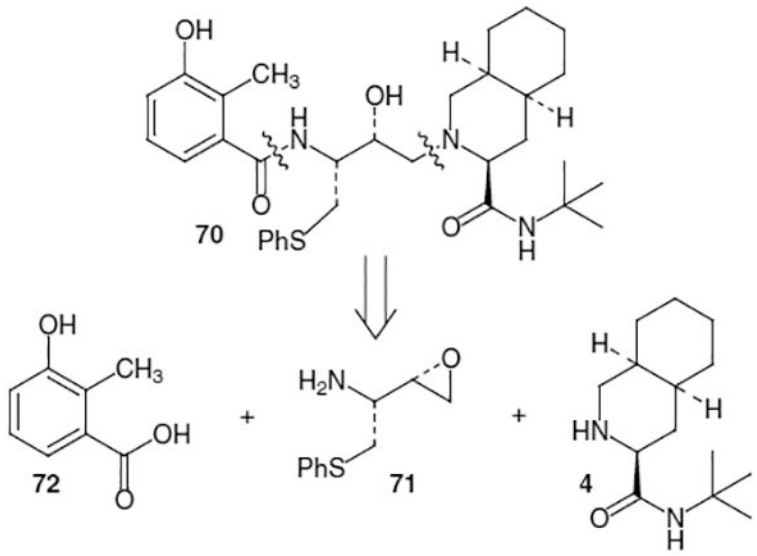


Figure 3.
Structure and Retrosynthesis of Nelfinavir (Viracept®, AG1343)

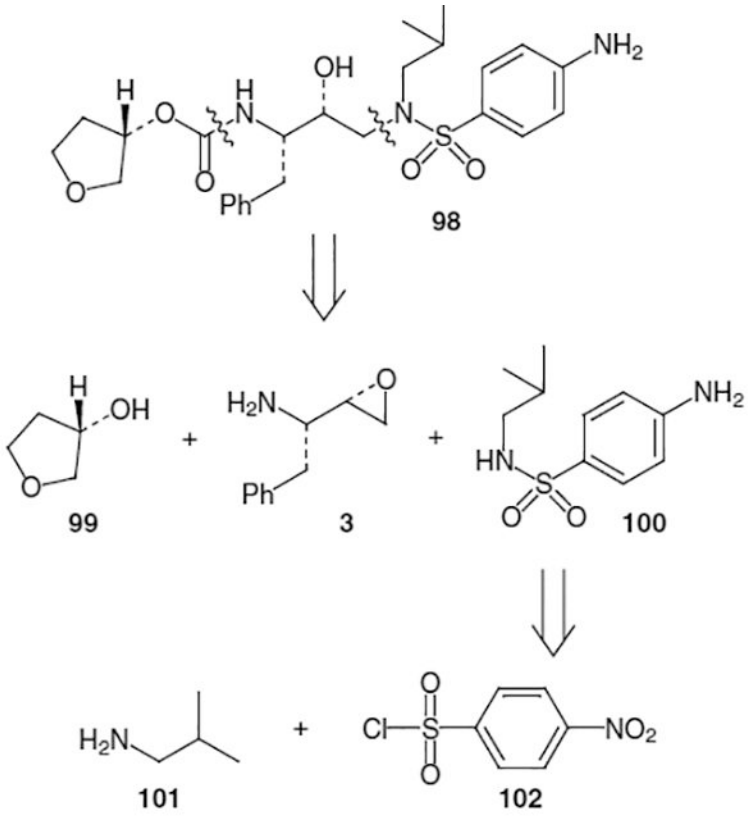


Figure 4.
Structure and Retrosynthesis of Amprenavir (Agenerase®, VX-478, 141W94)

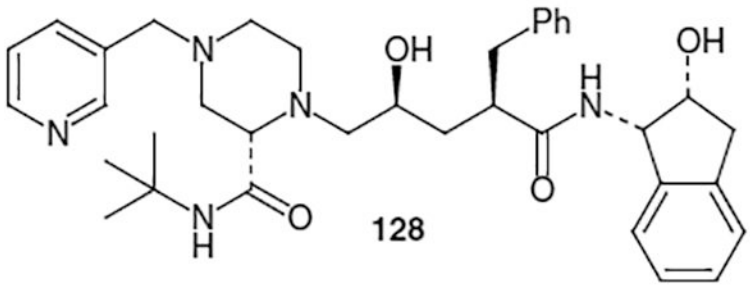


Figure 5.
Structure of Indinavir (Crixivan®, L-735,524, MK-639)

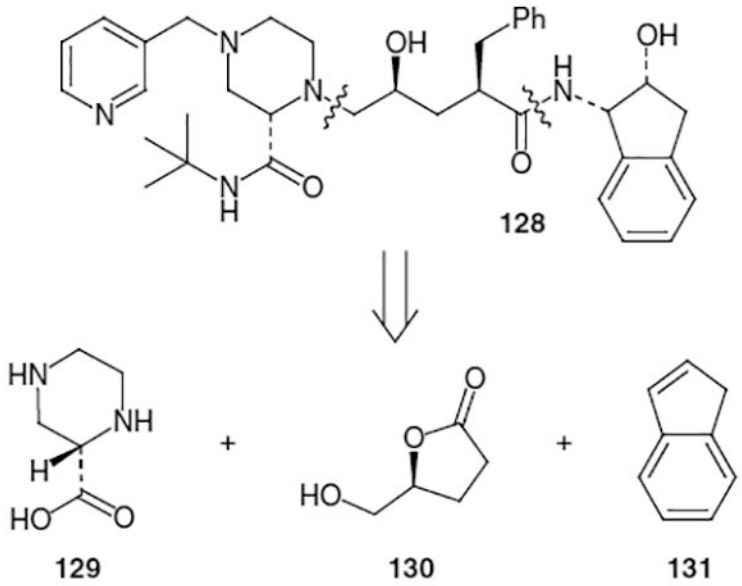


Figure 6.
Retrosynthesis of Indinavir Fragments (Merck)

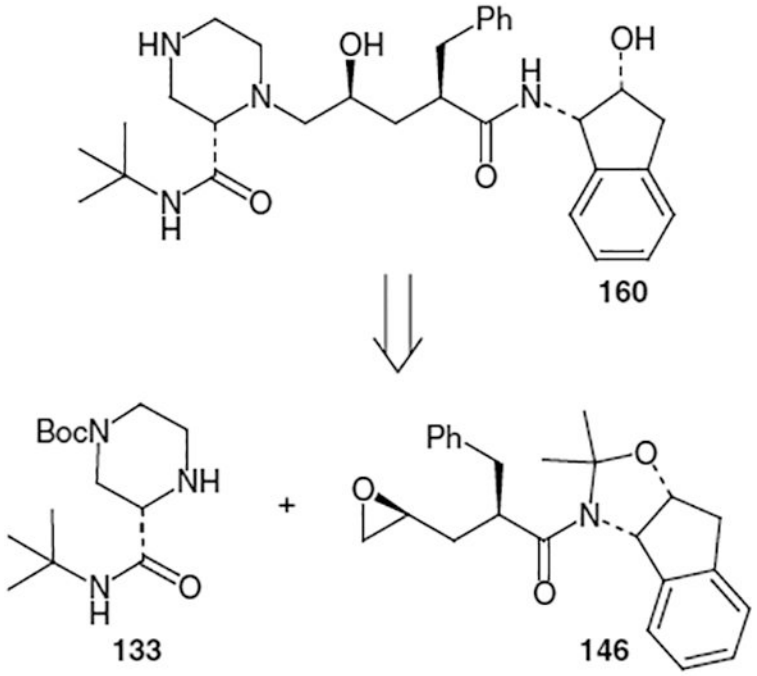


Figure 7.
Coupling of Epoxide for Indinavir Synthesis

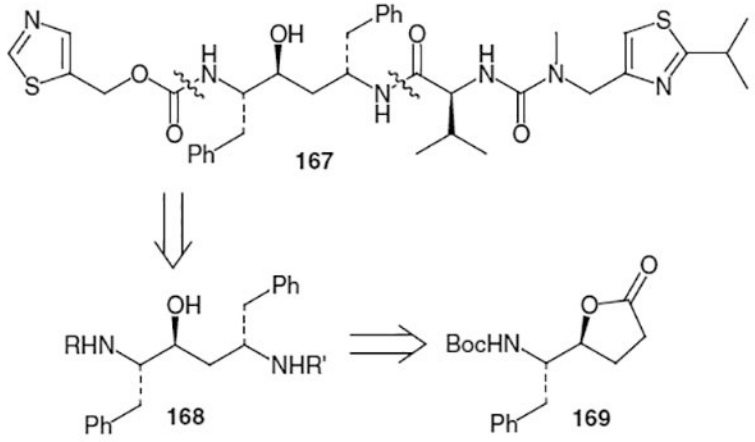


Figure 8.
Structure of Ritonavir **167** (Norvir®, ABT-538) and Retrosynthesis of Isostere Fragment **168**

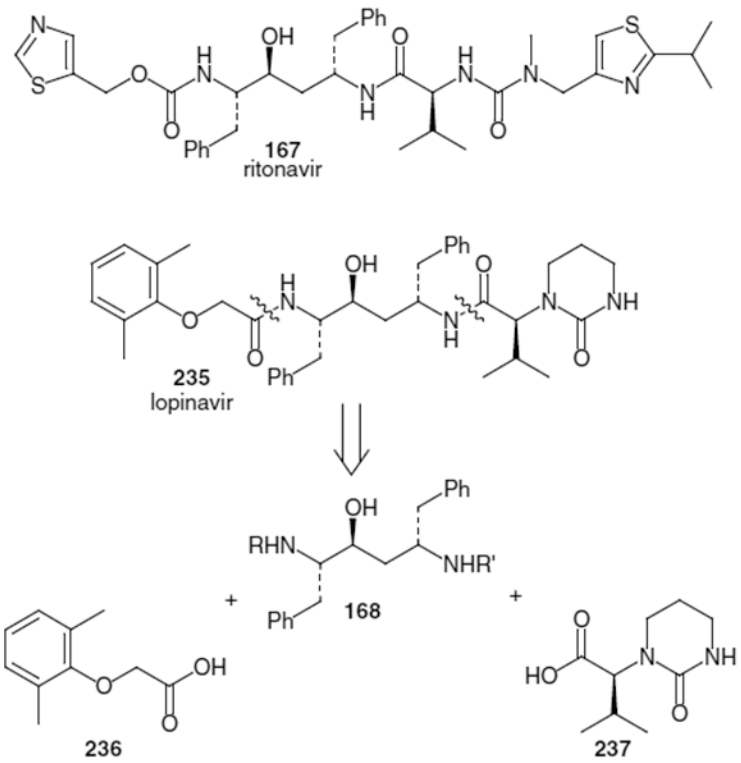
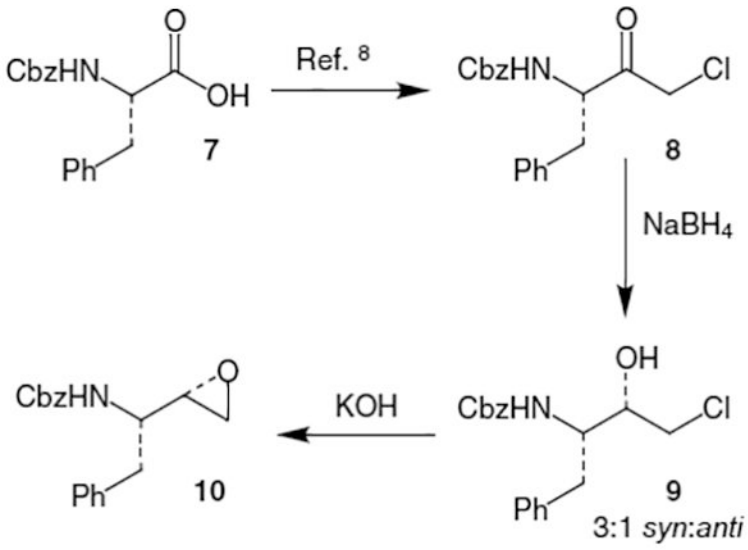
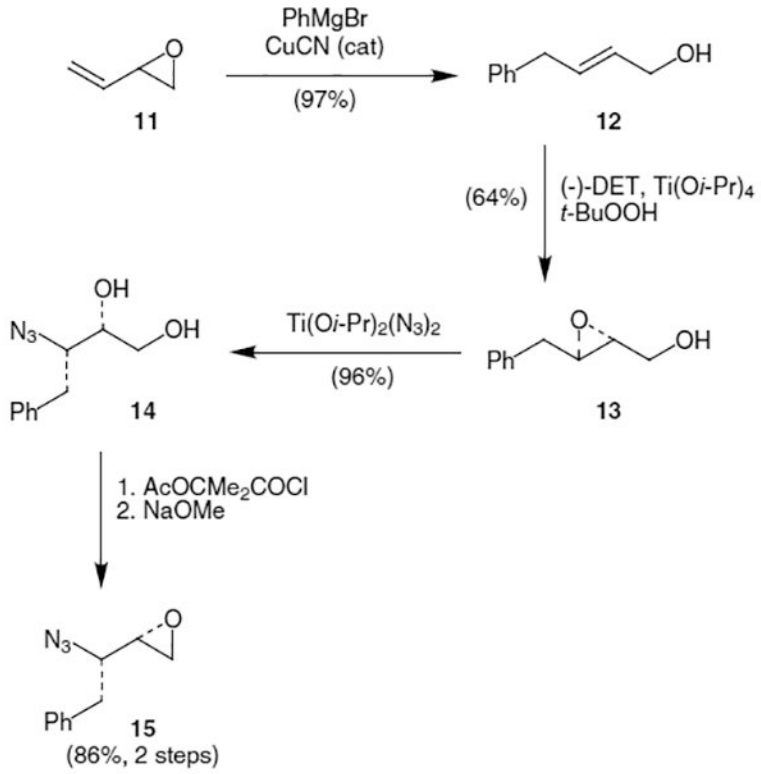


Figure 9.

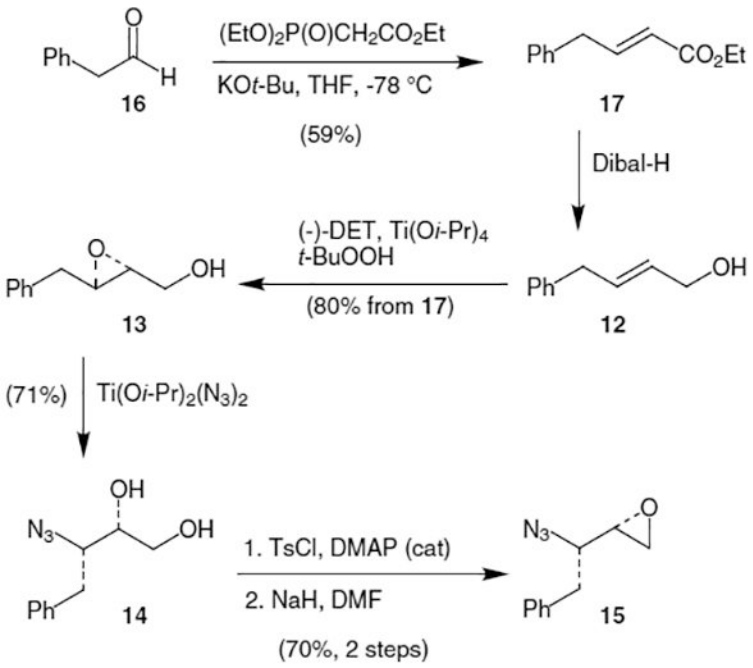
Structures of Ritonavir **167** (Norvir®, ABT-538), Lopinavir **235** (Aluviran®, ABT-378, Component of Kaletra®) and Retrosynthesis of Lopinavir



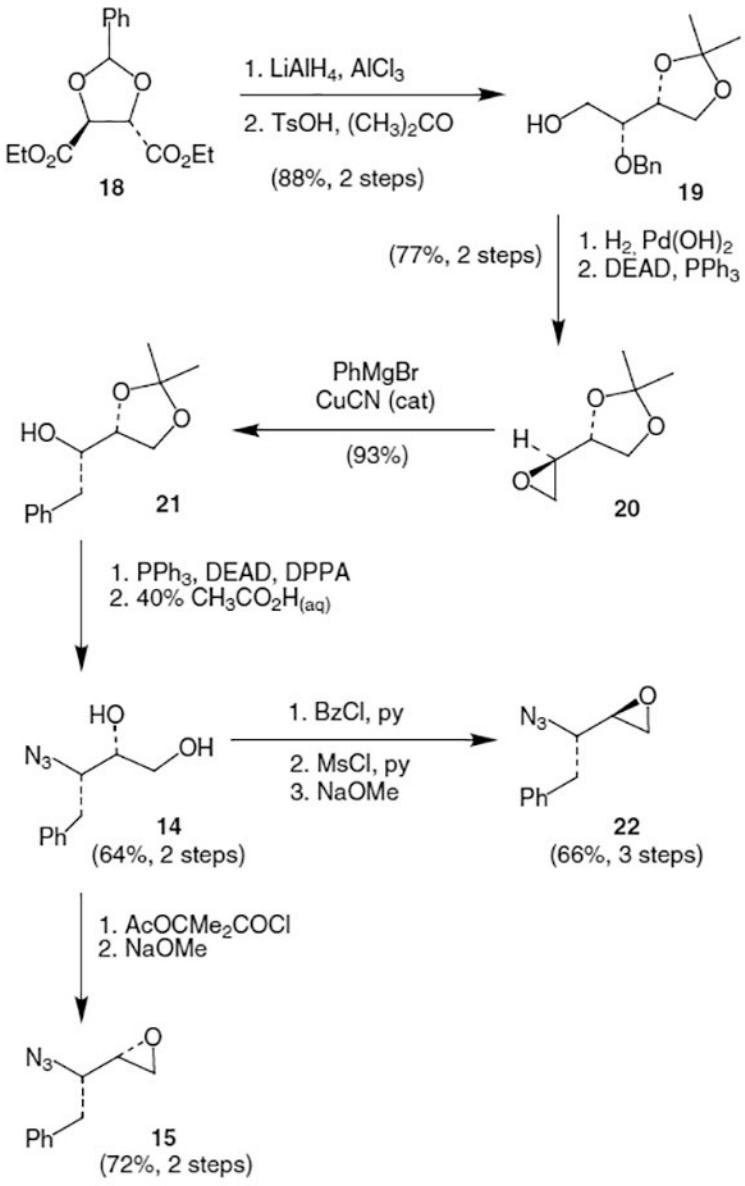
Scheme 1.



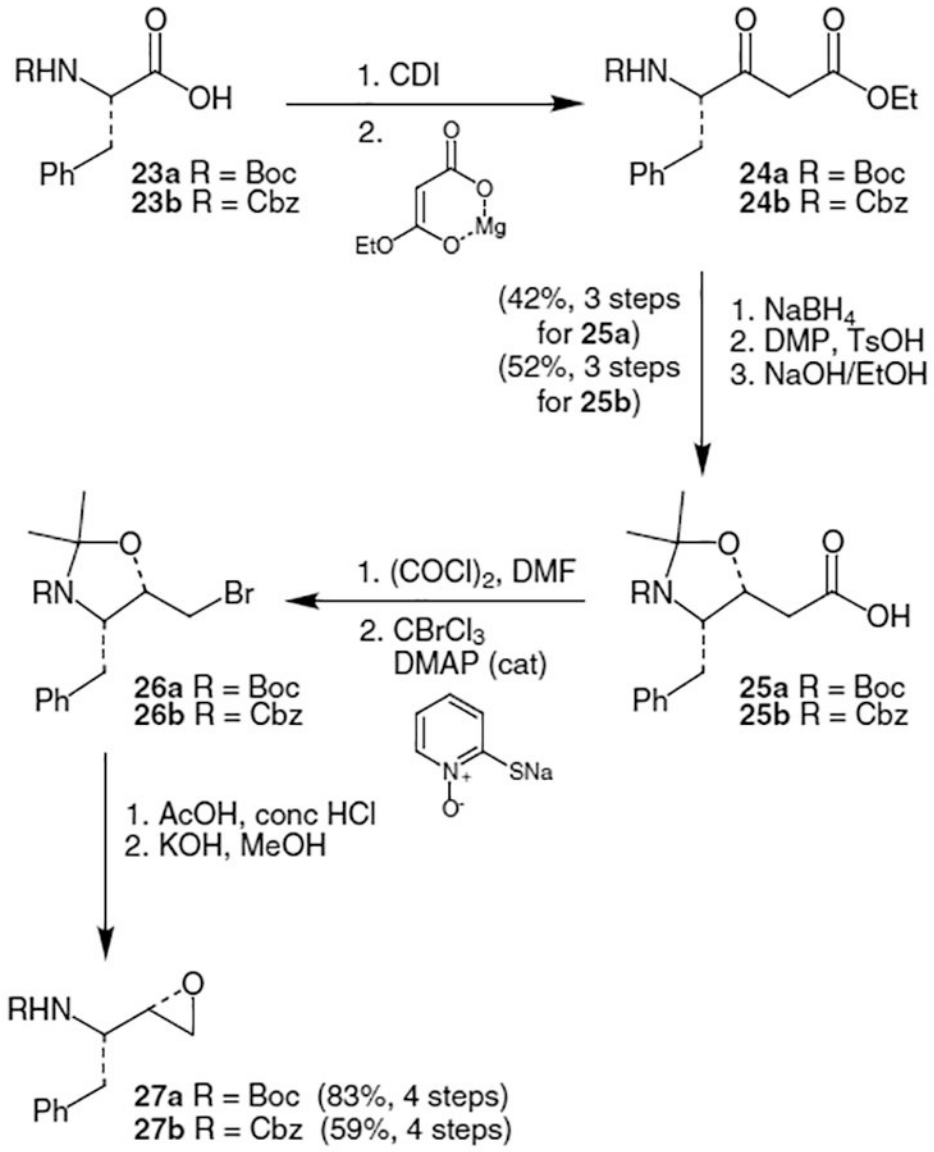
Scheme 2.



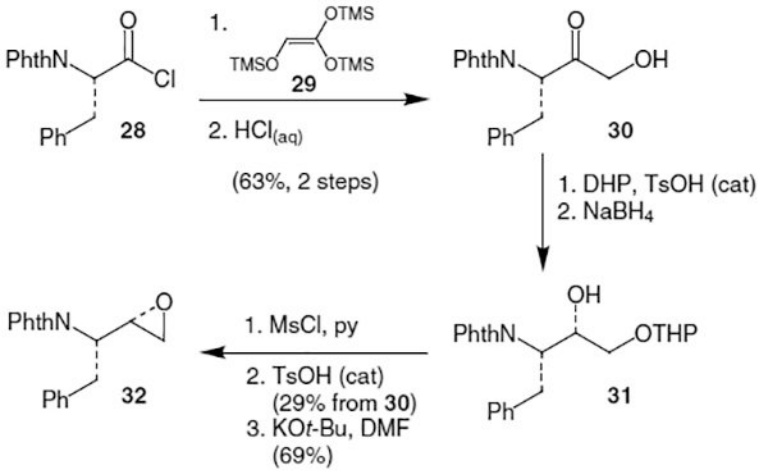
Scheme 3.



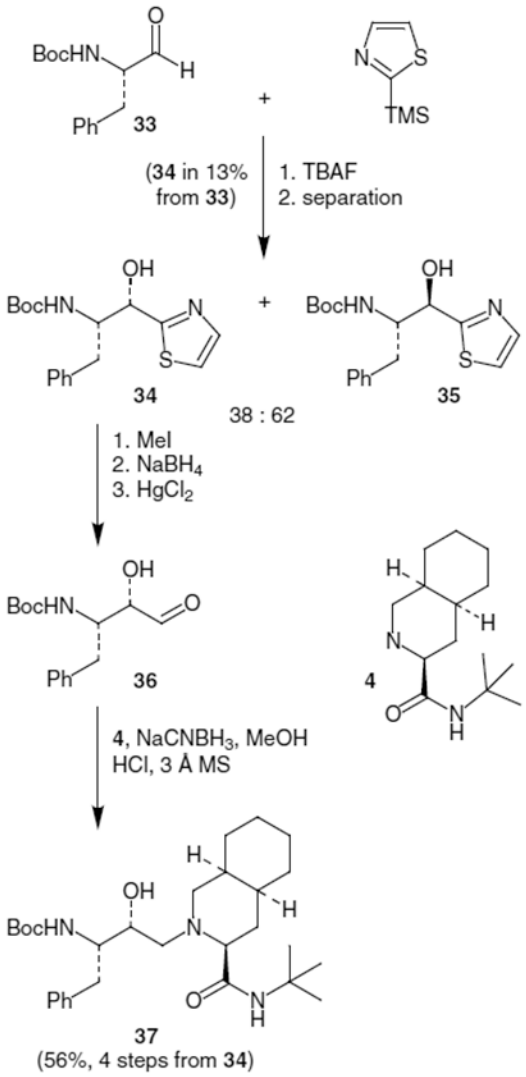
Scheme 4.



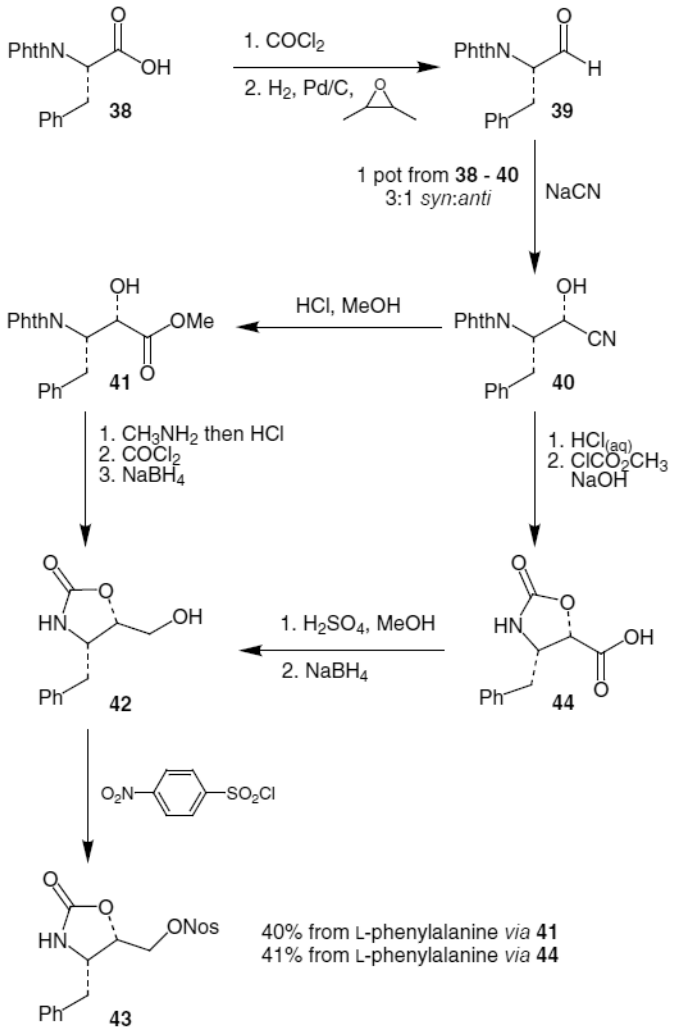
Scheme 5.



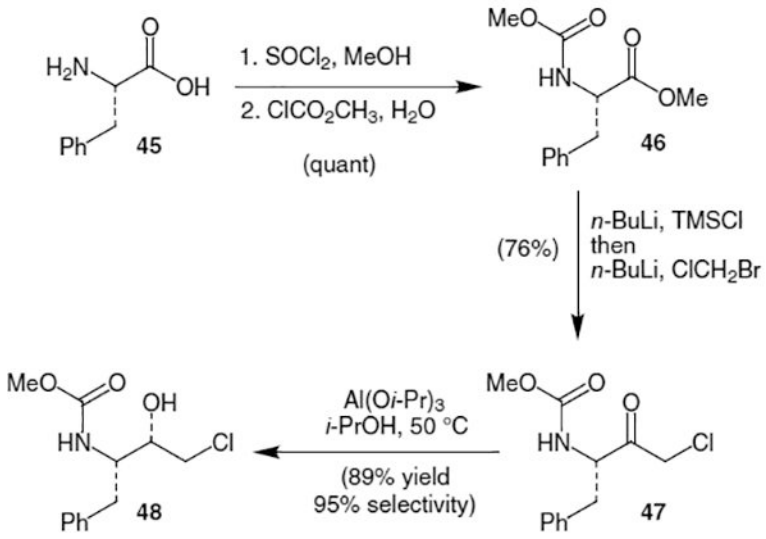
Scheme 6.



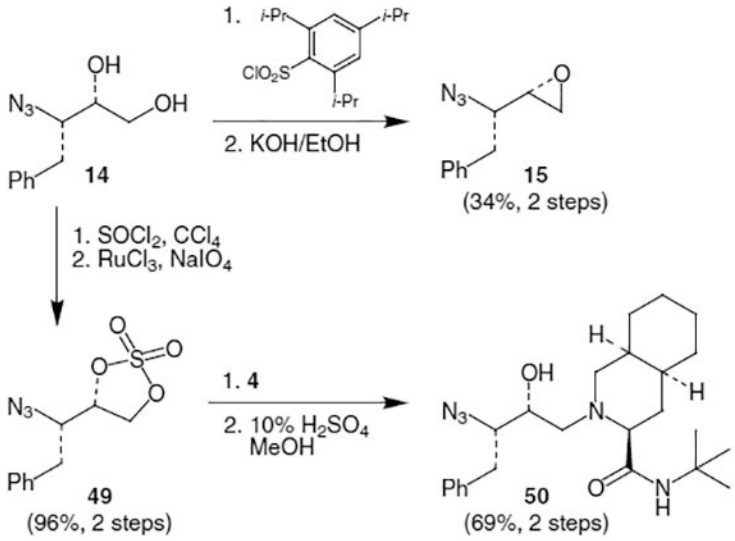
Scheme 7.



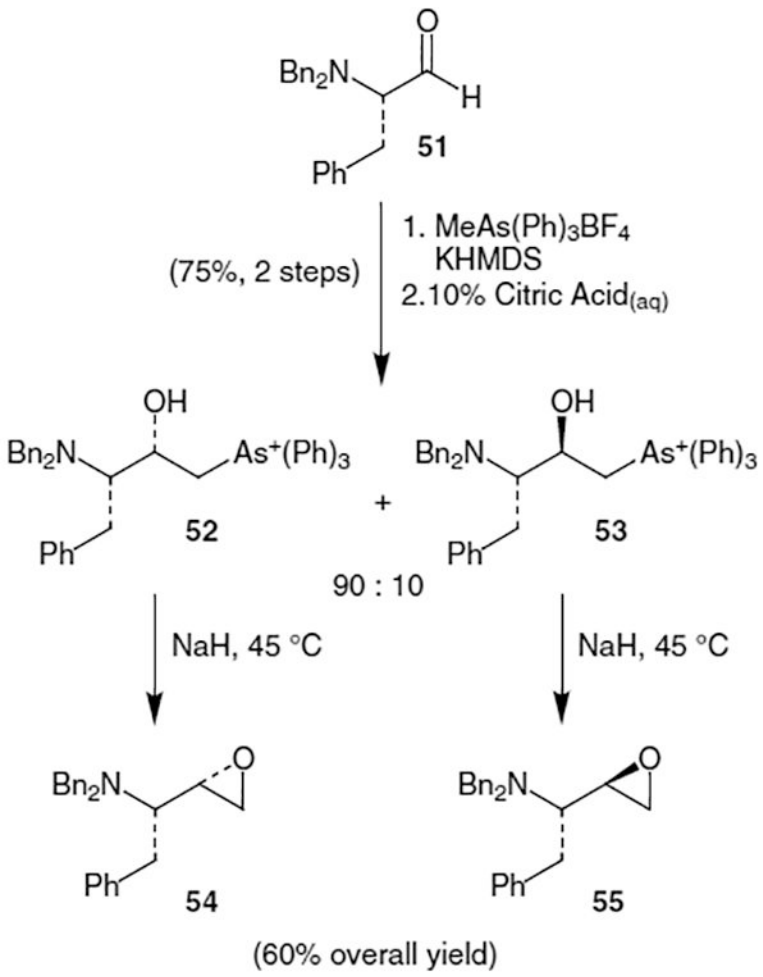
Scheme 8.



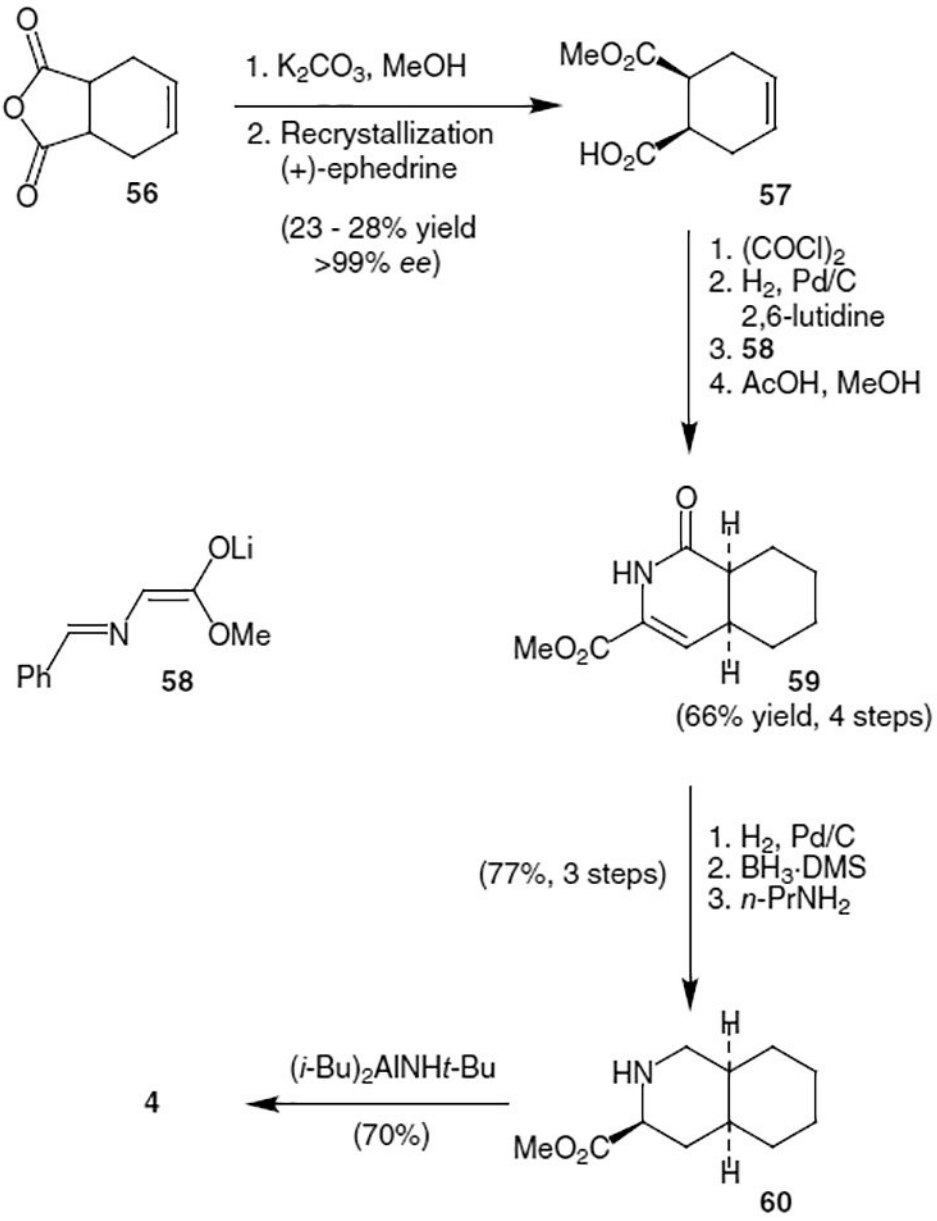
Scheme 9.



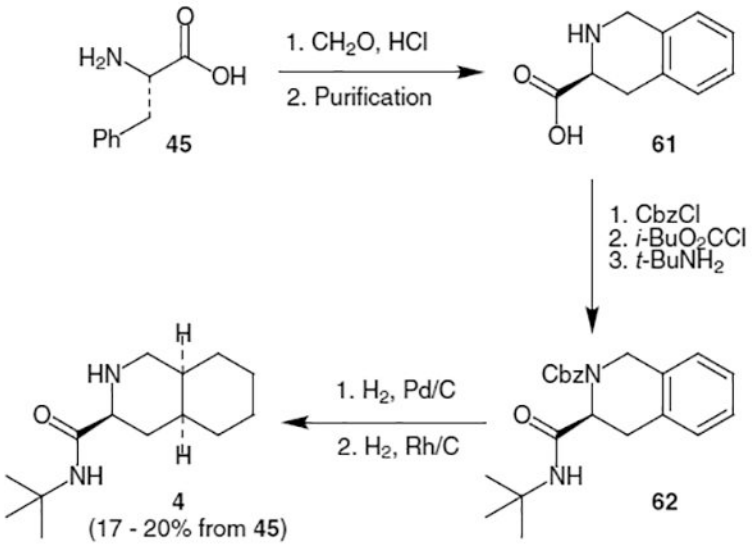
Scheme 10.



Scheme 11.



Scheme 12.



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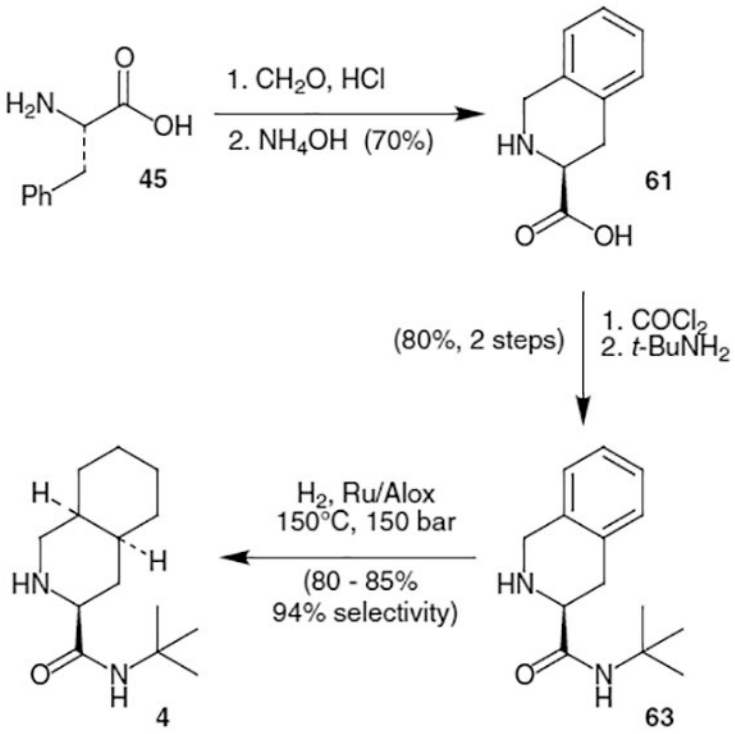

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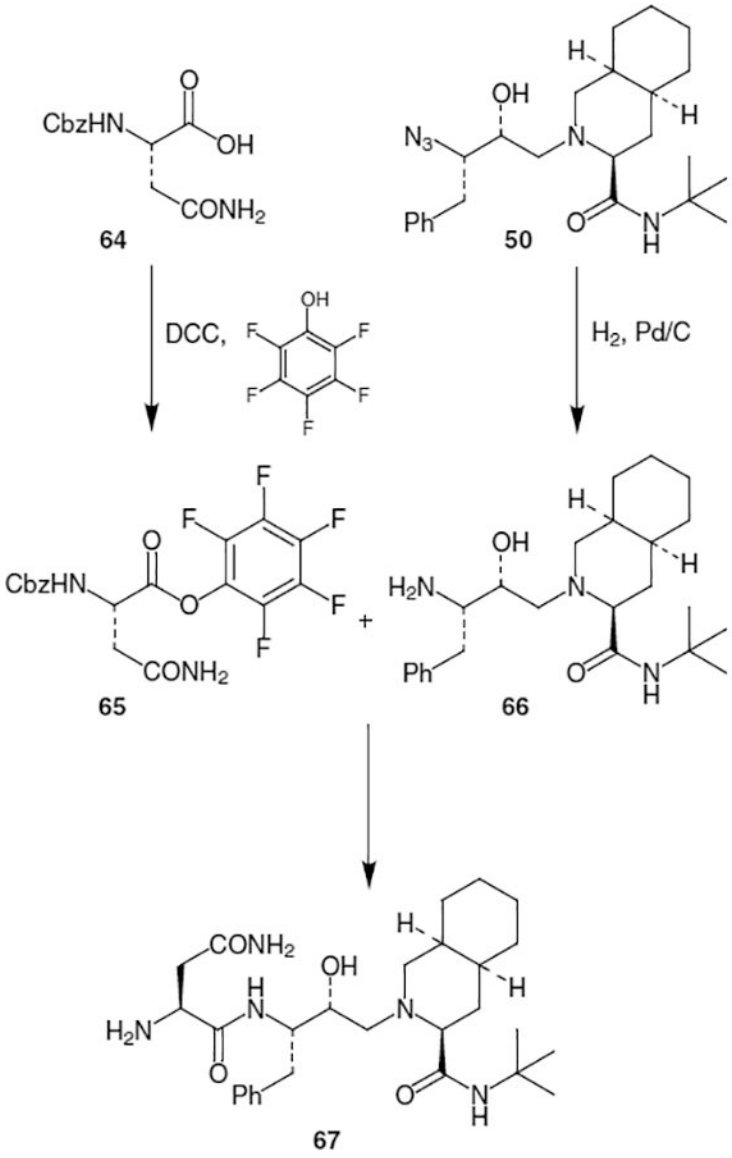

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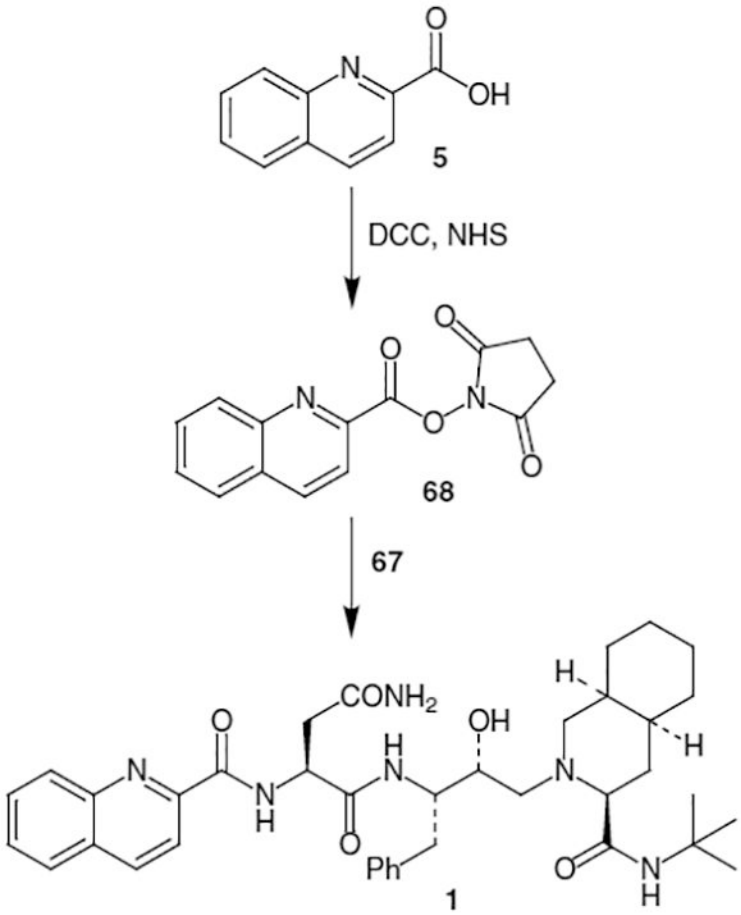

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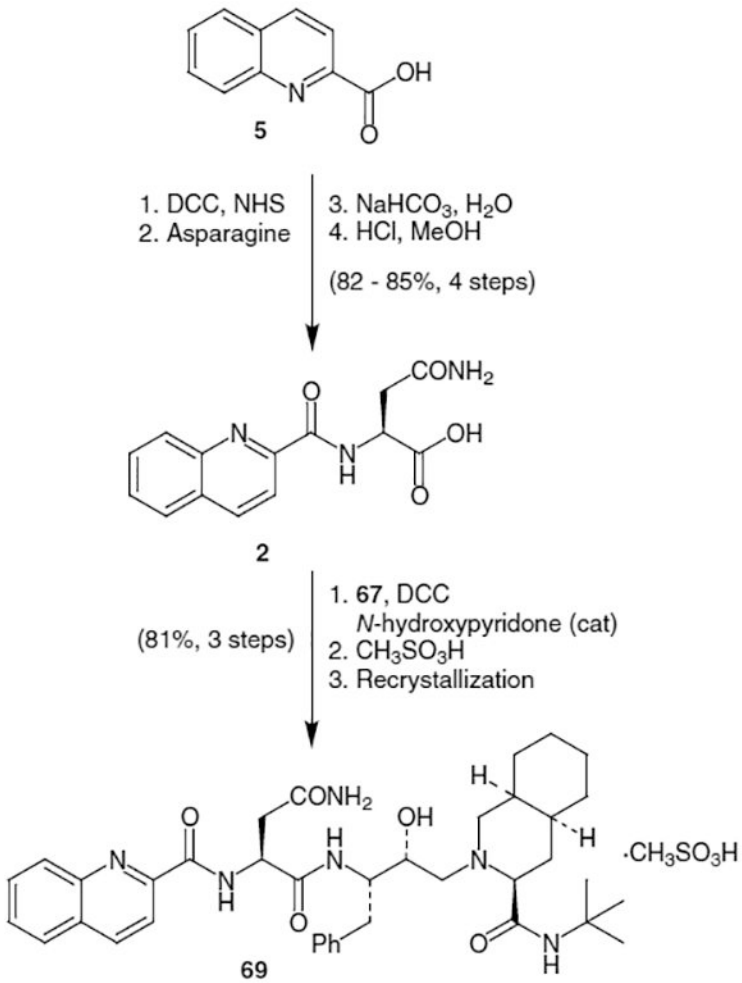

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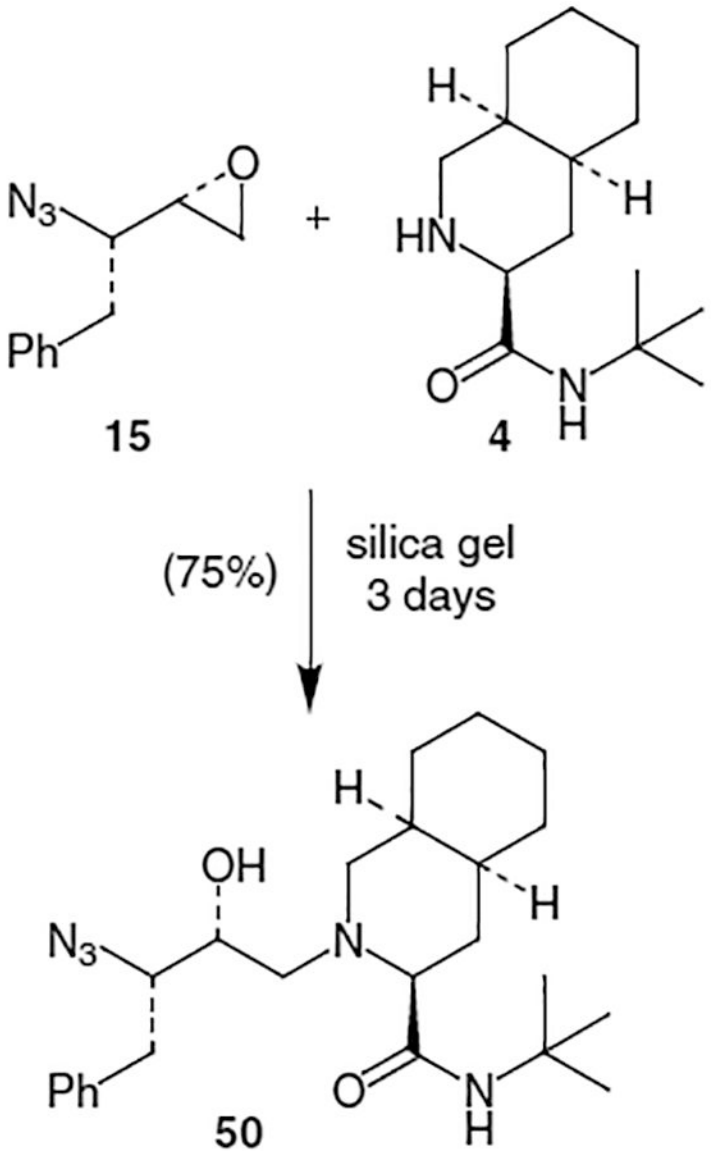

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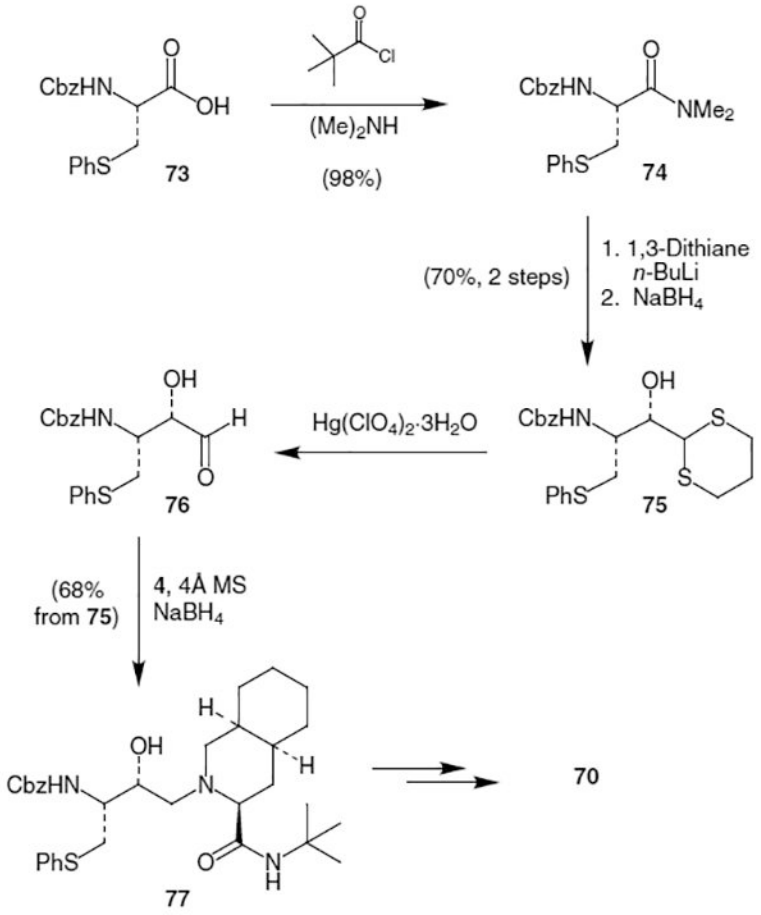

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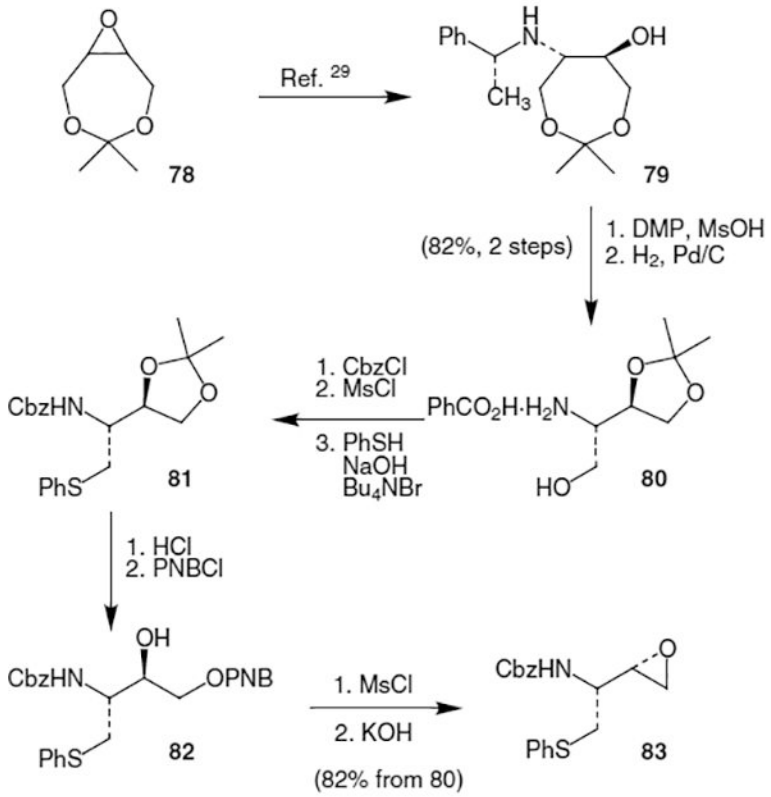

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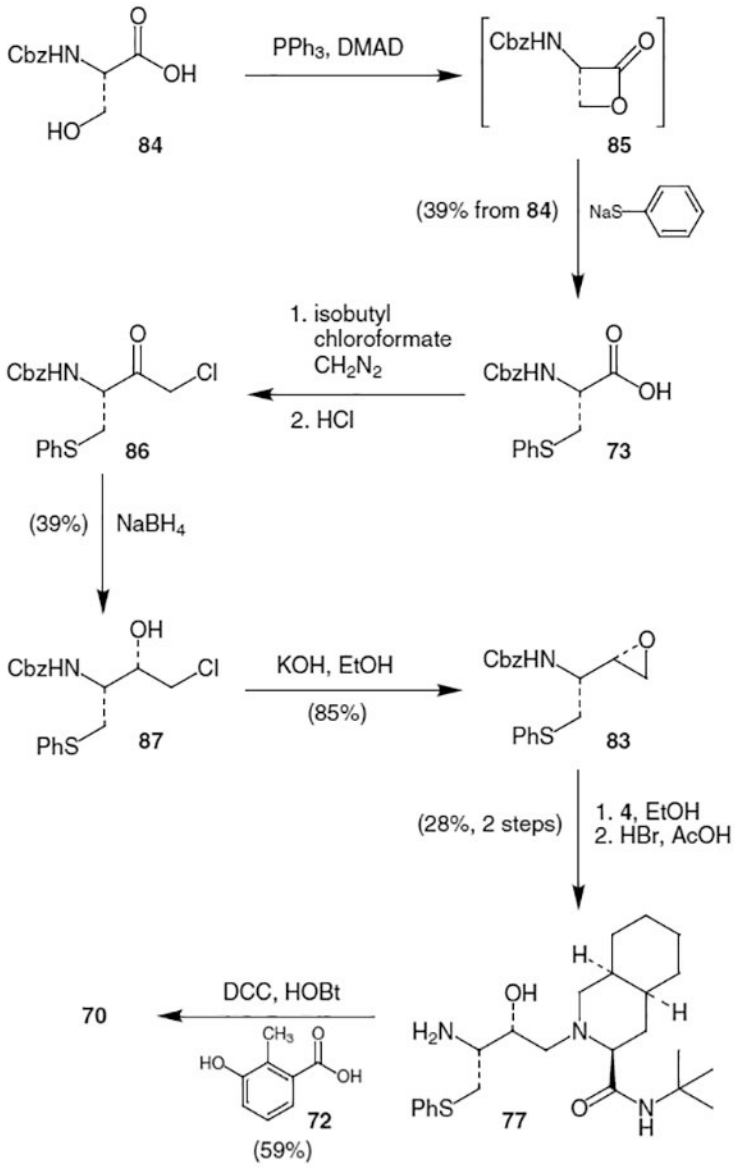

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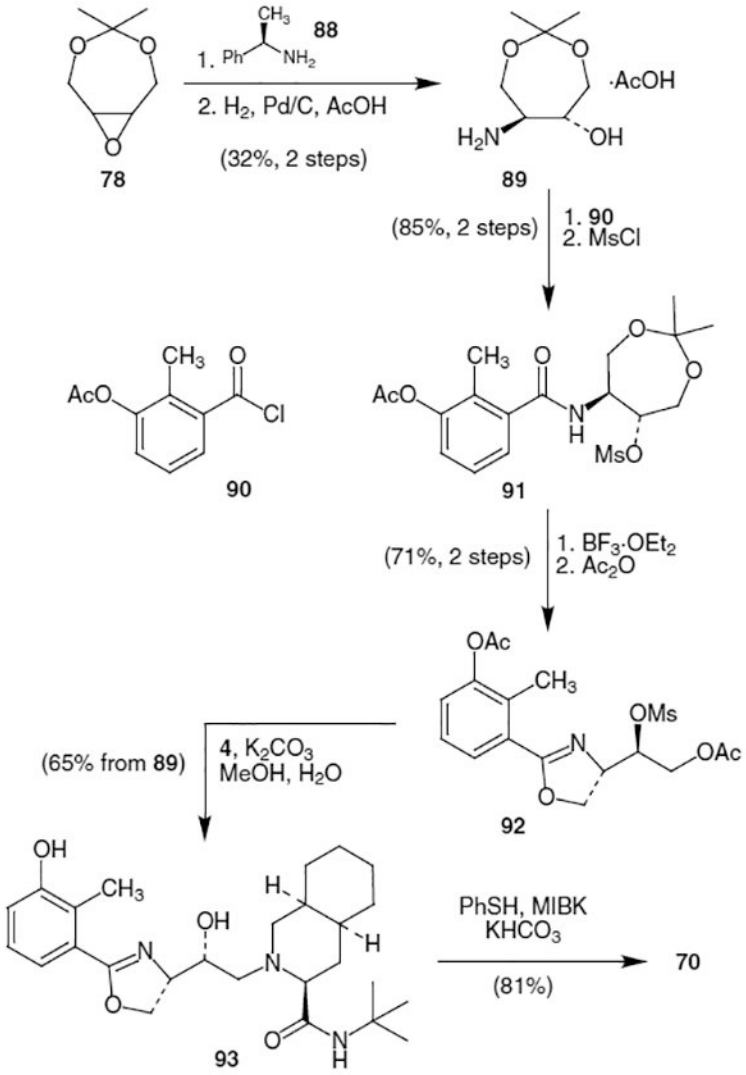

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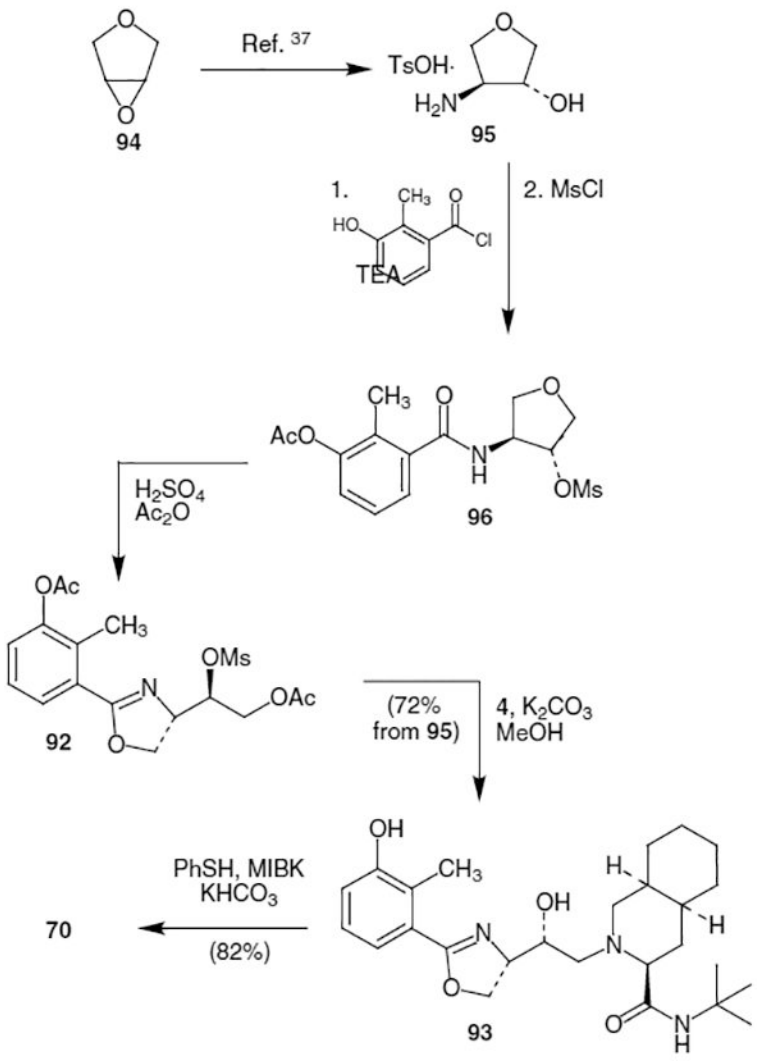

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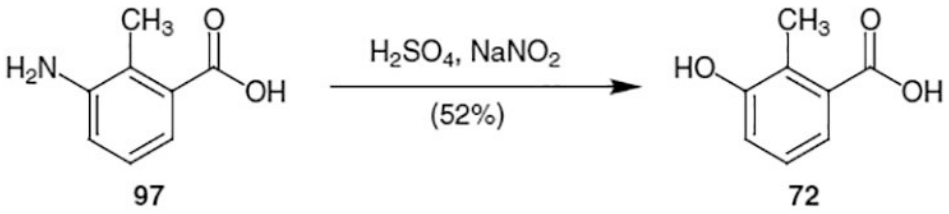

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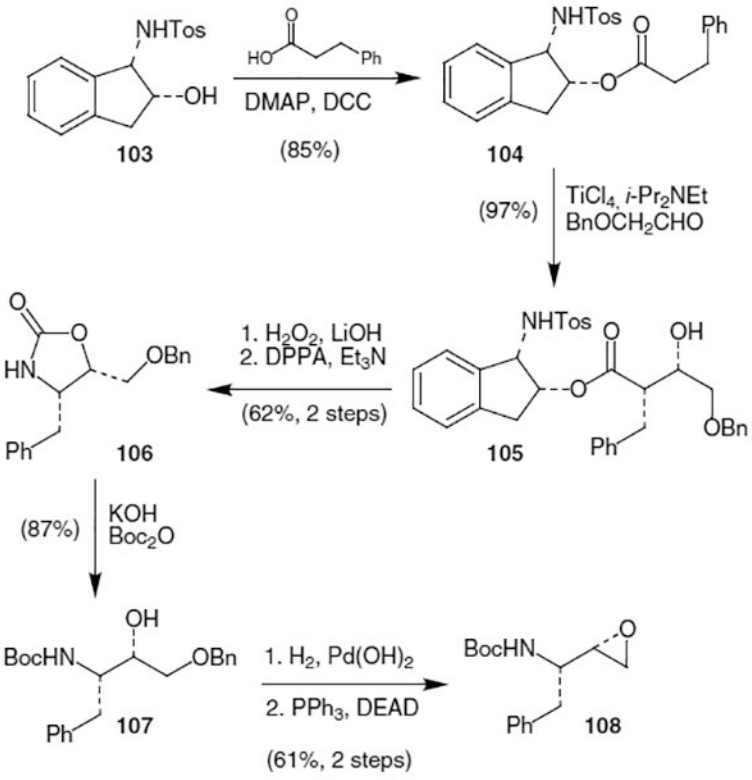

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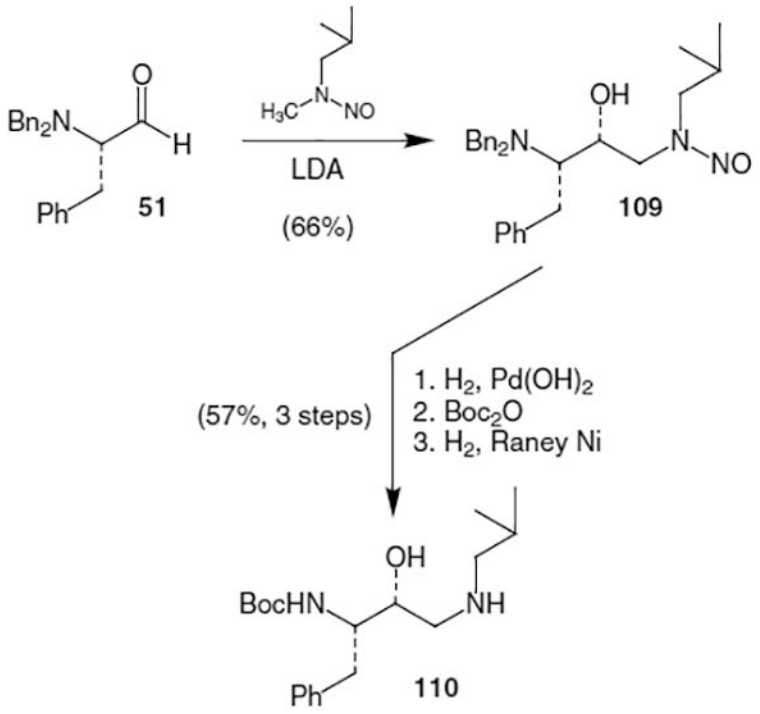

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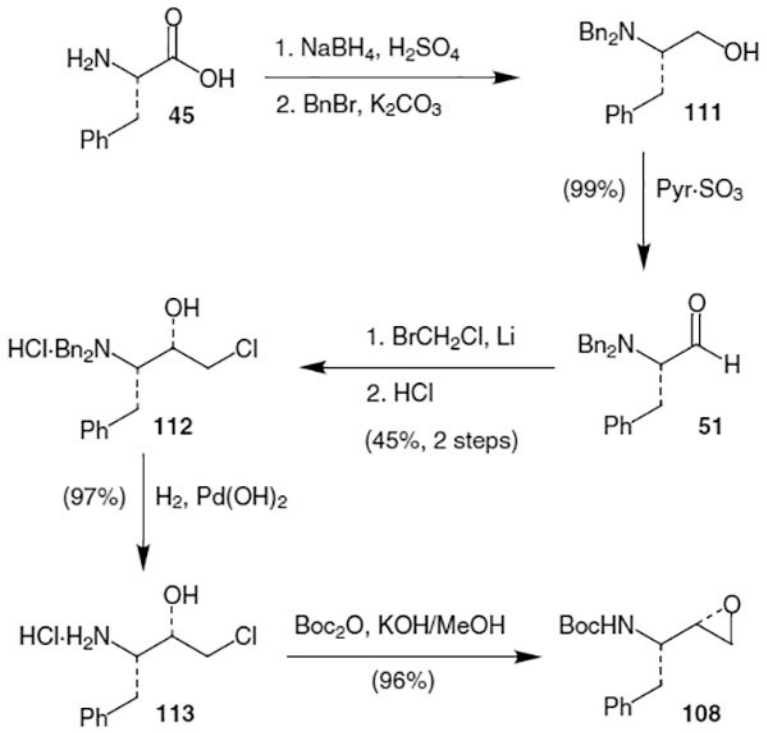

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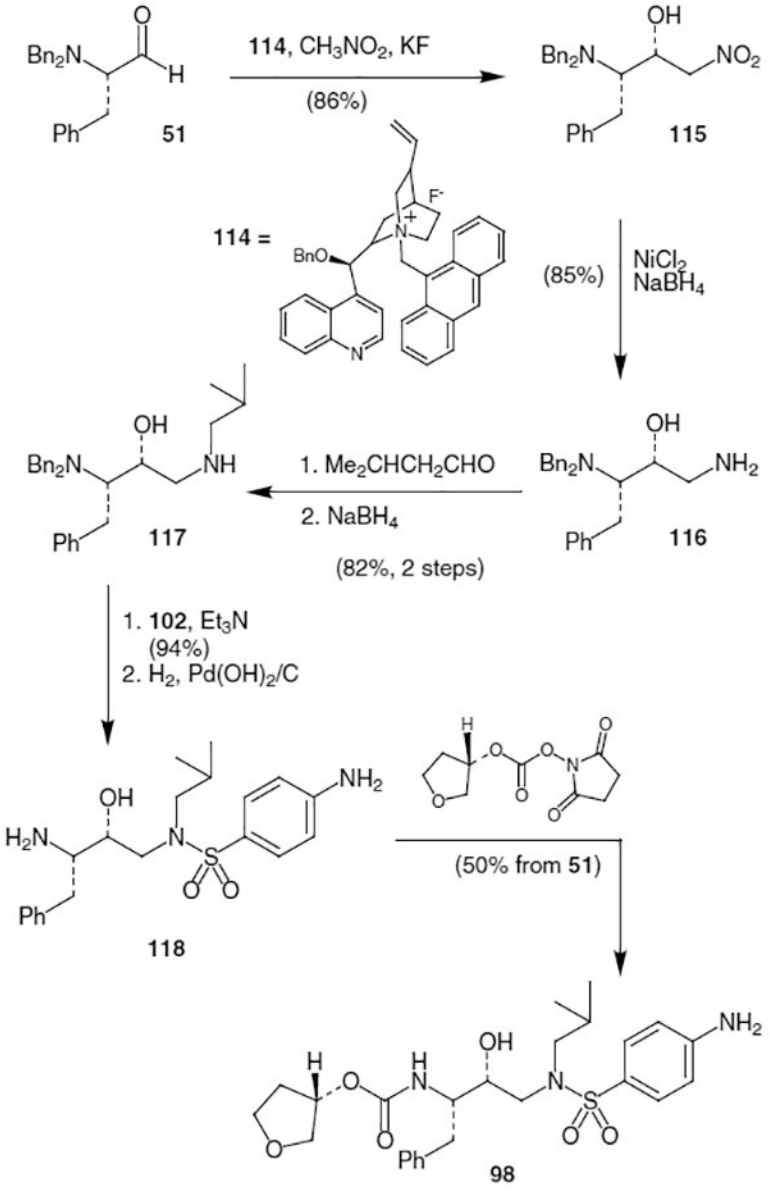

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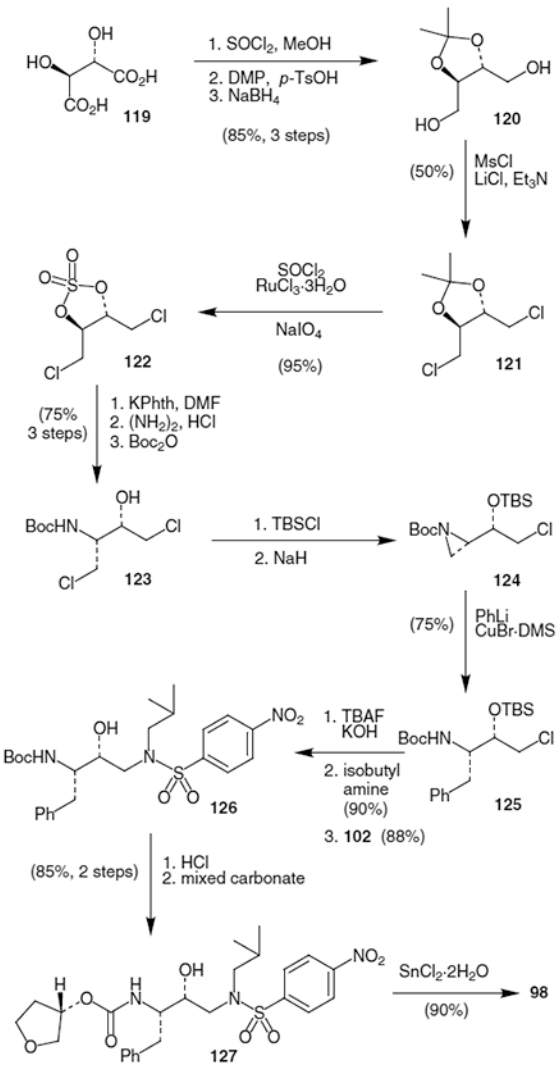

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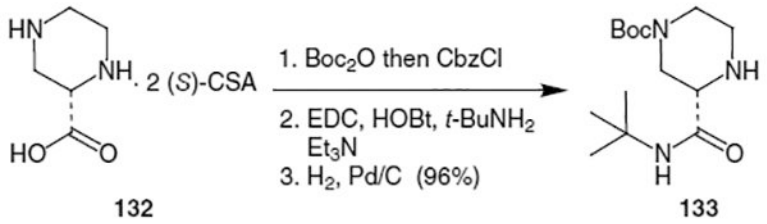

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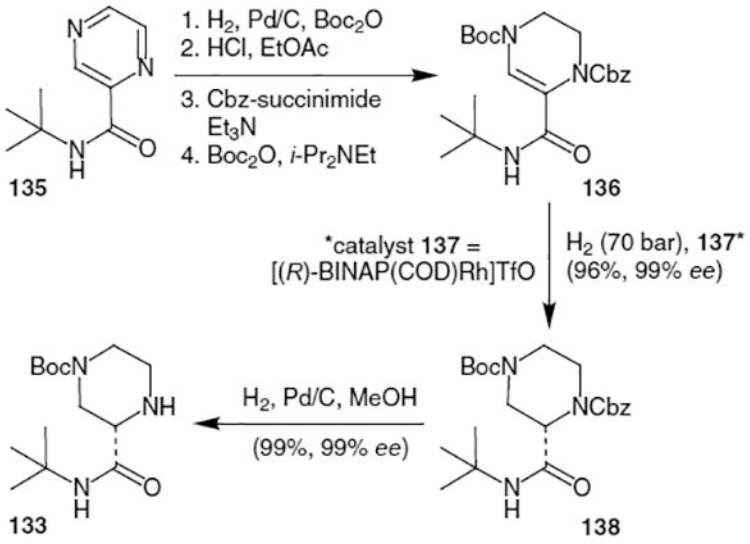
Scheme 30.

Scheme 31.



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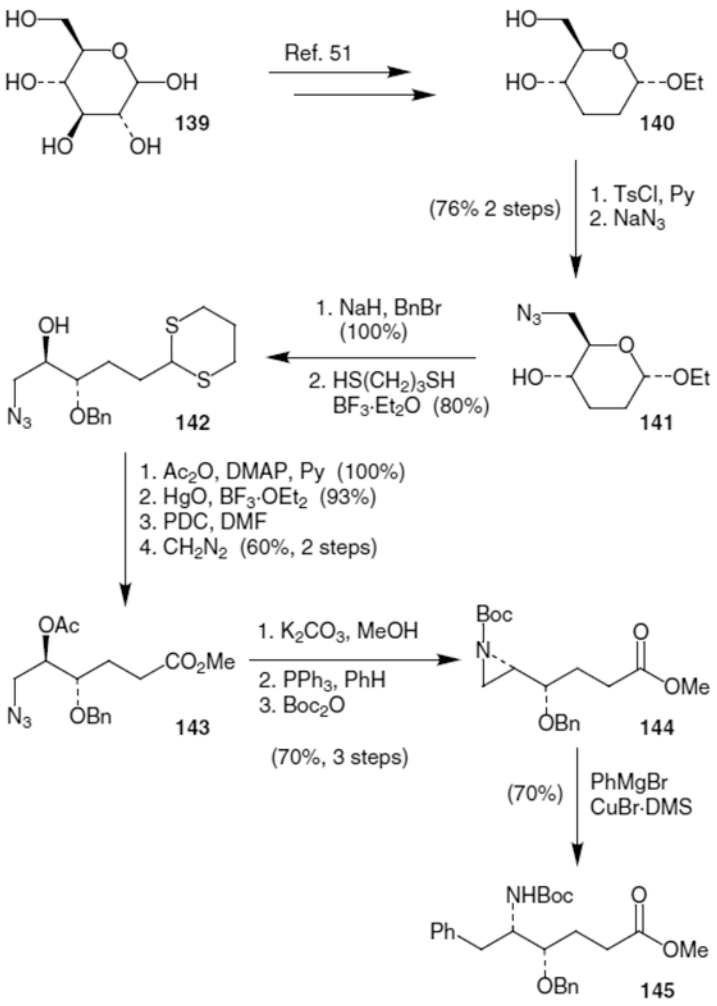

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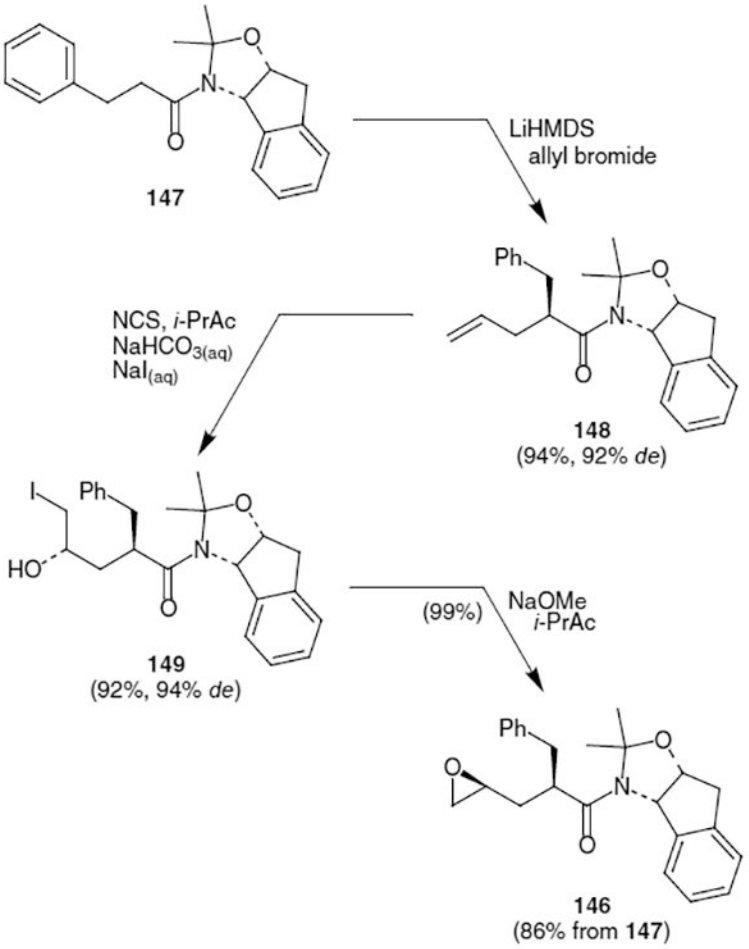

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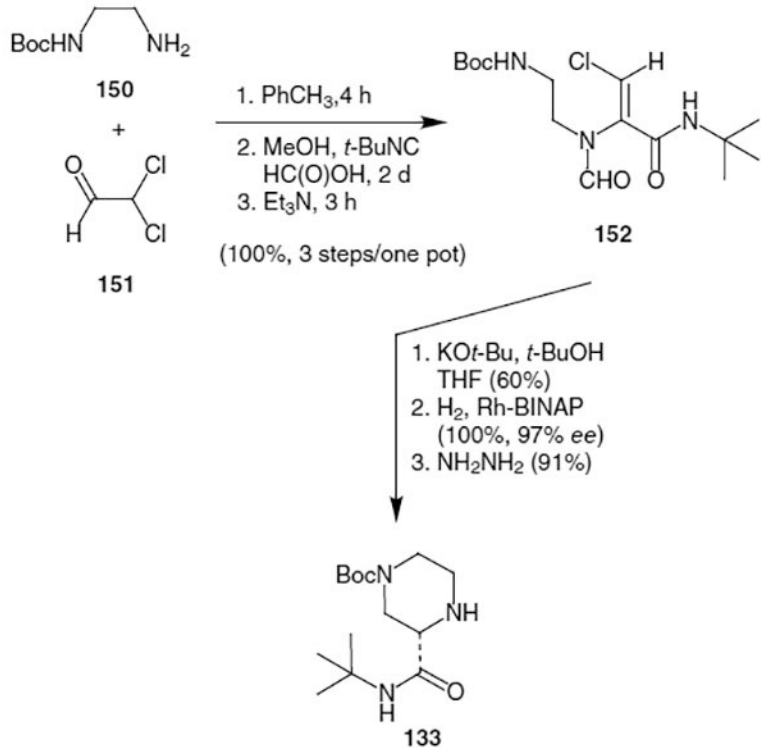

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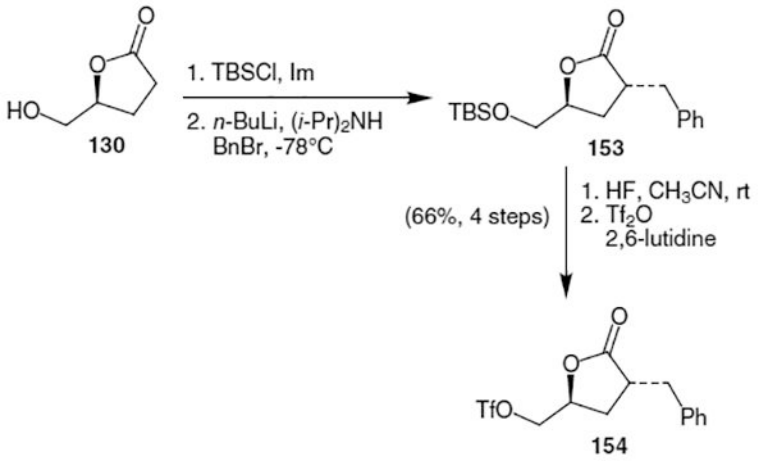

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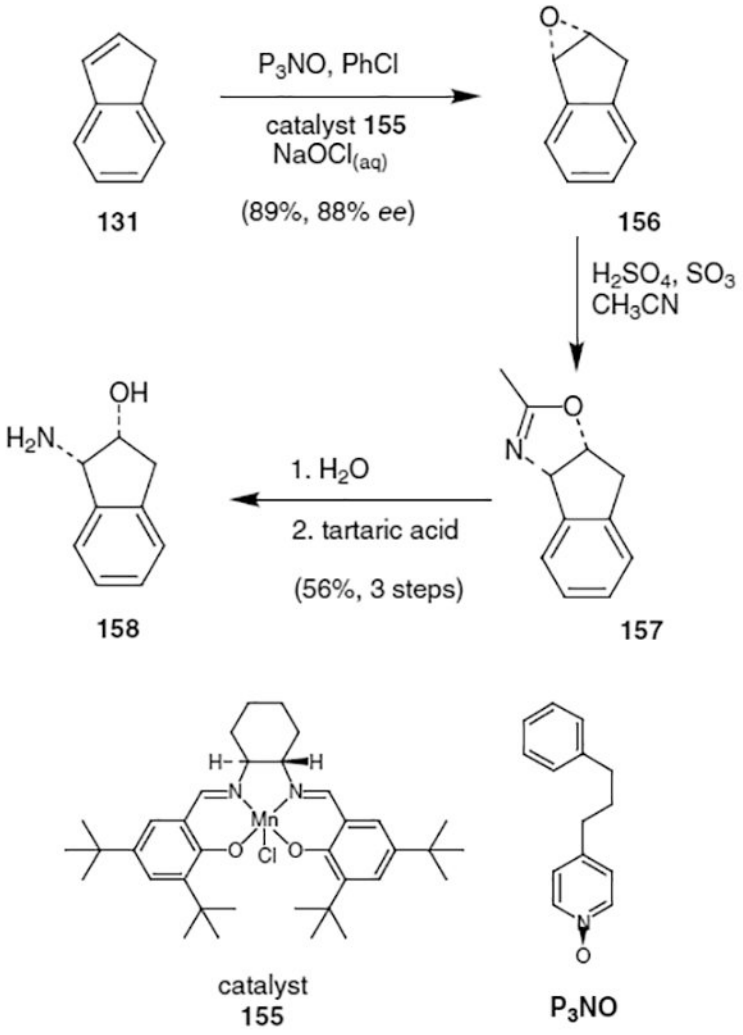

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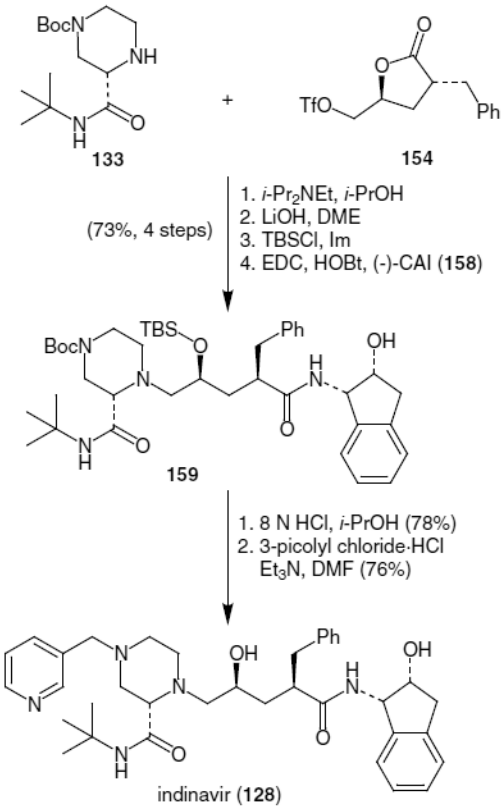

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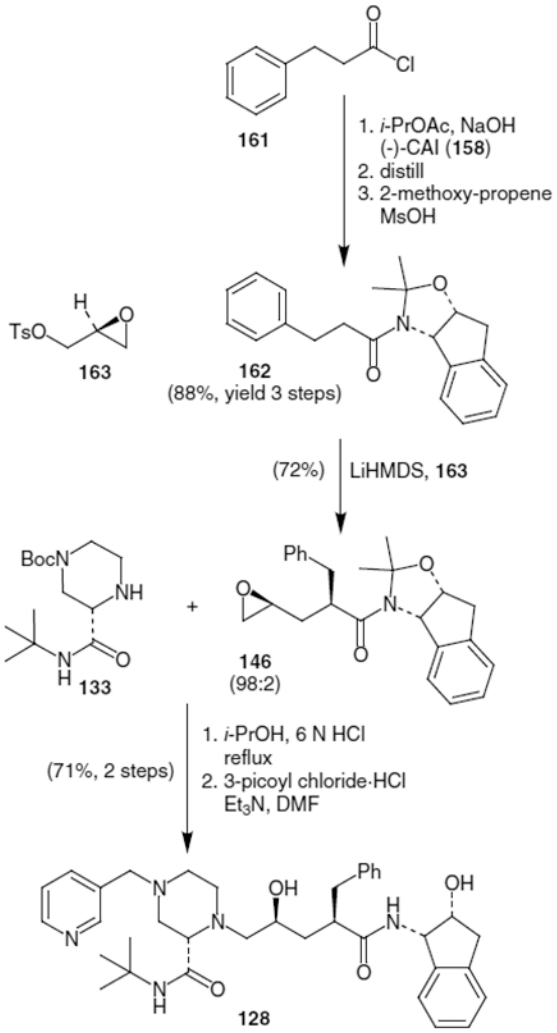

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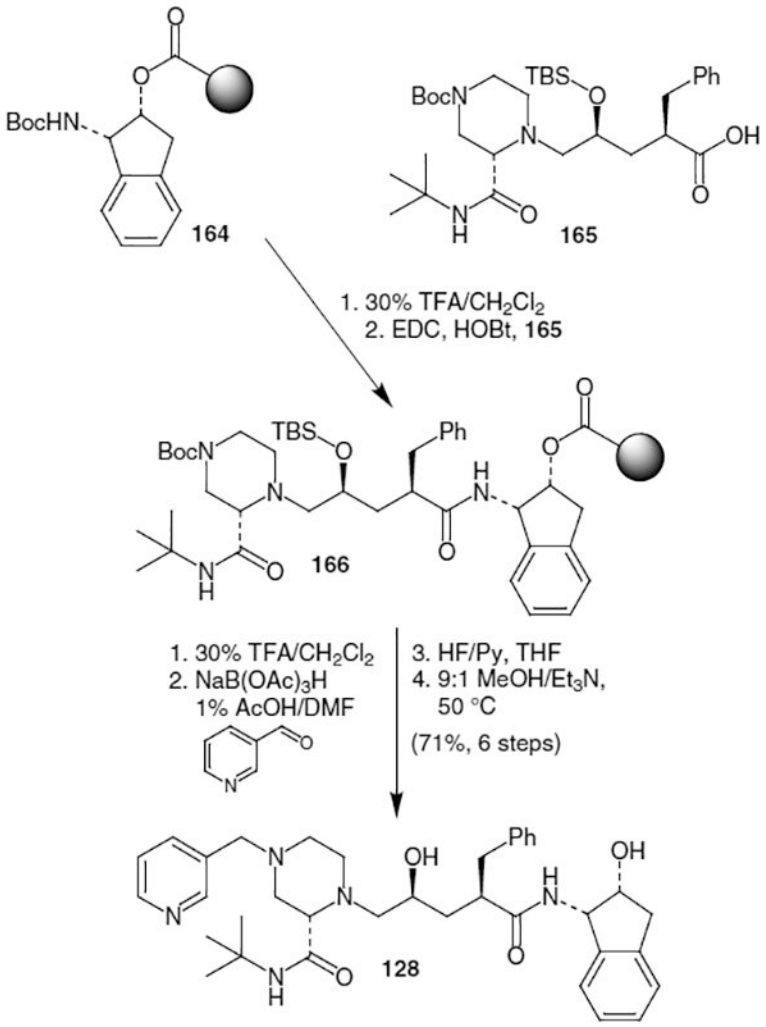

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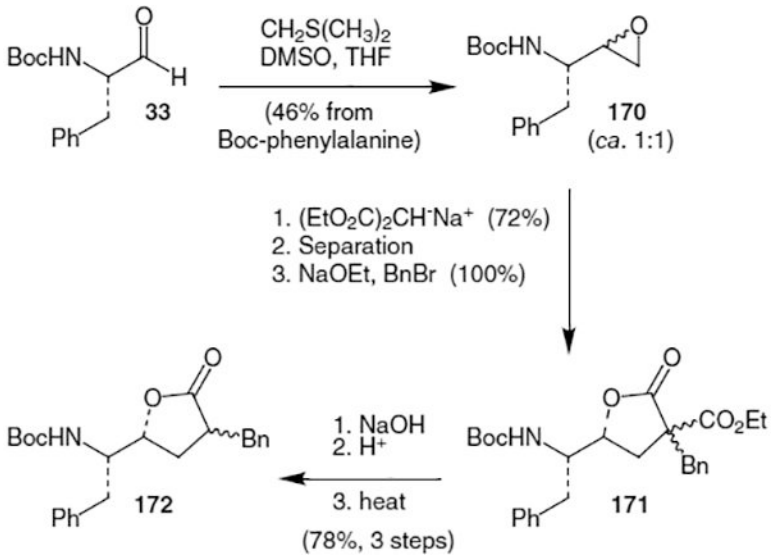

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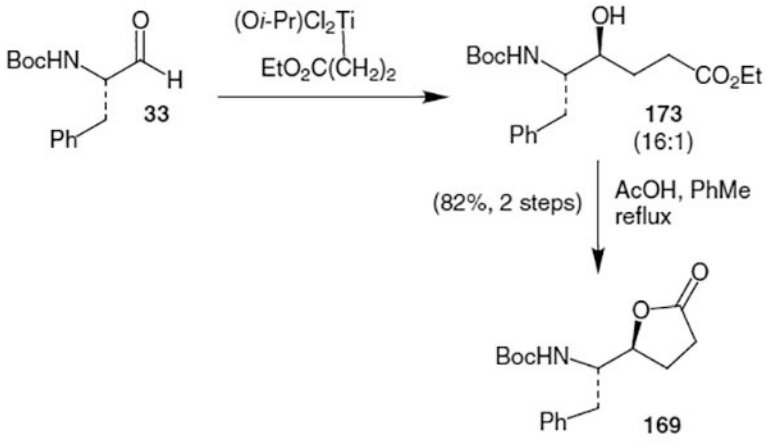

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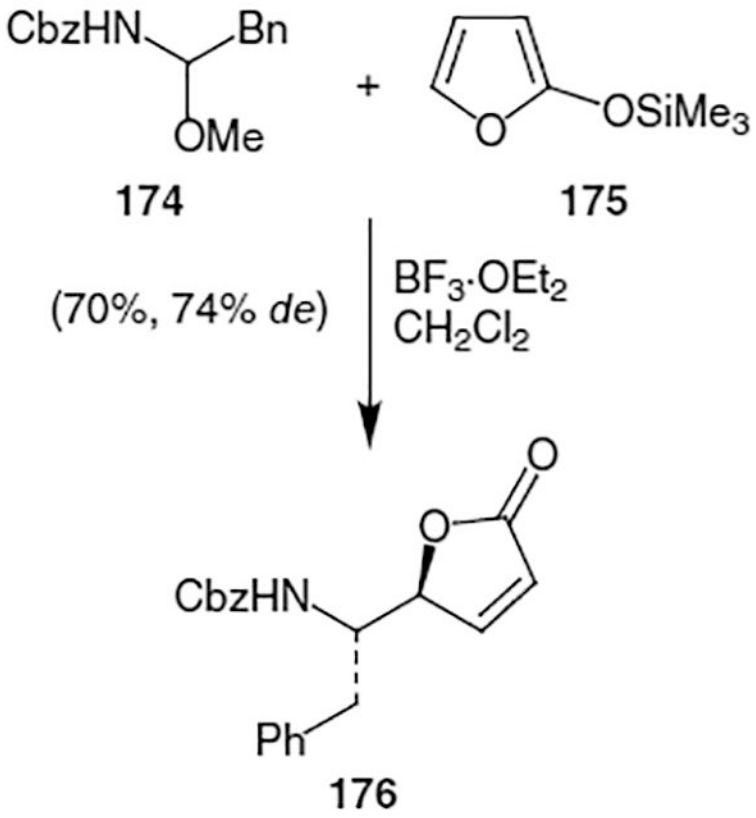

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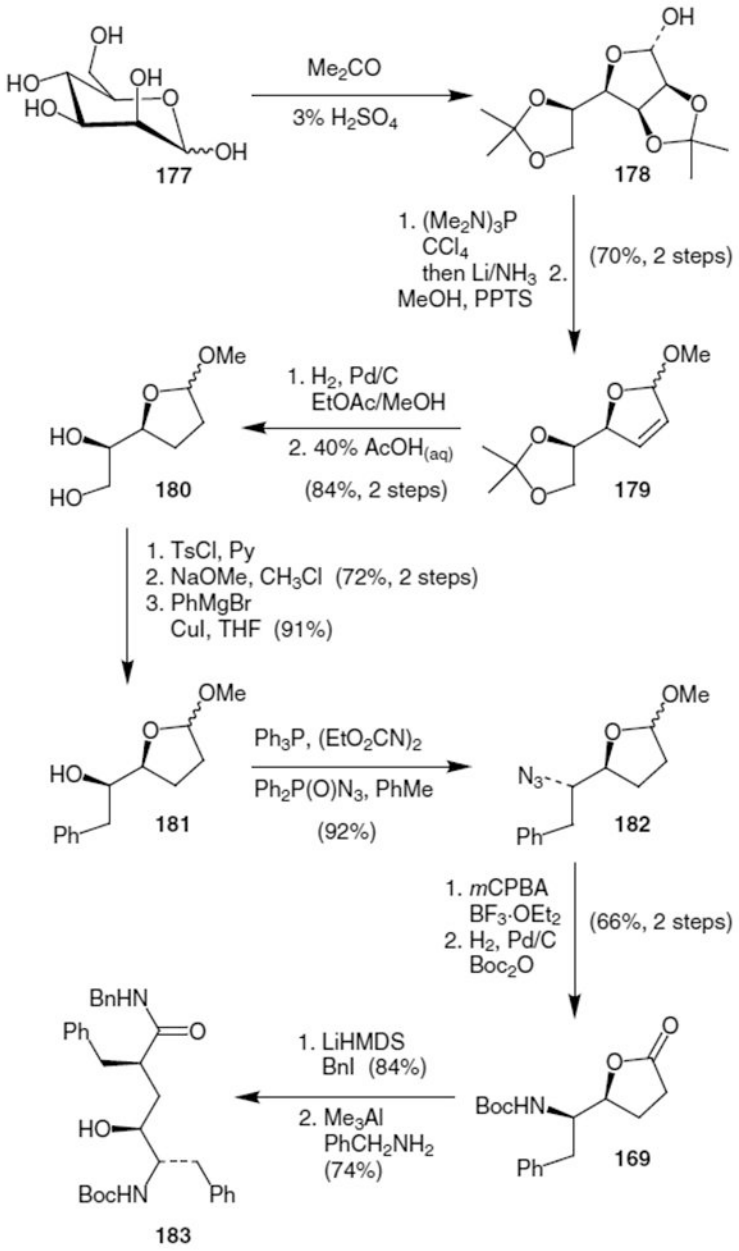

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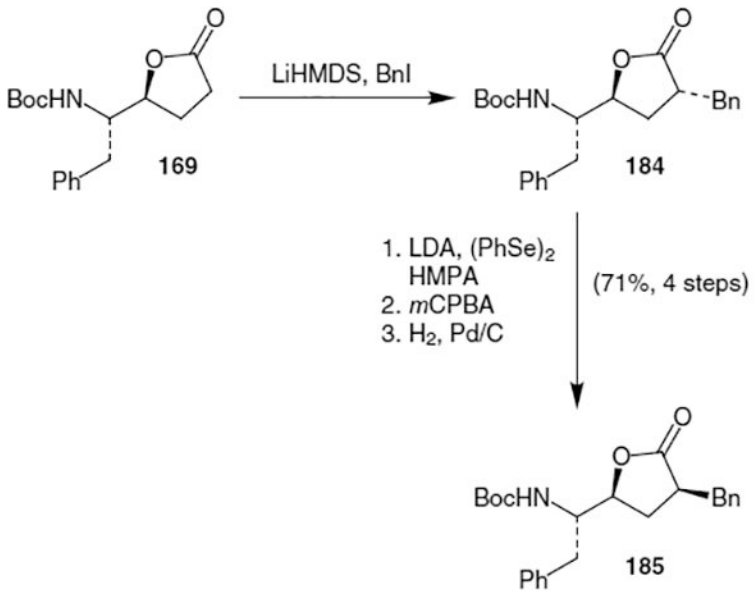

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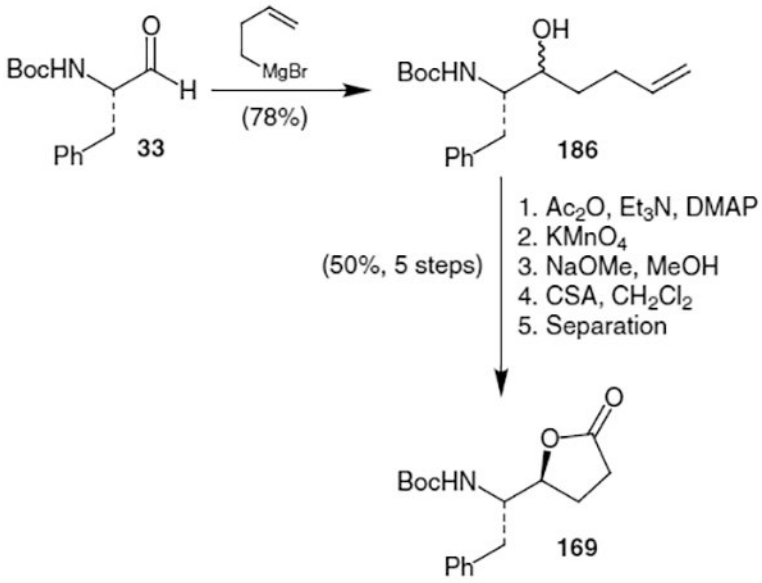

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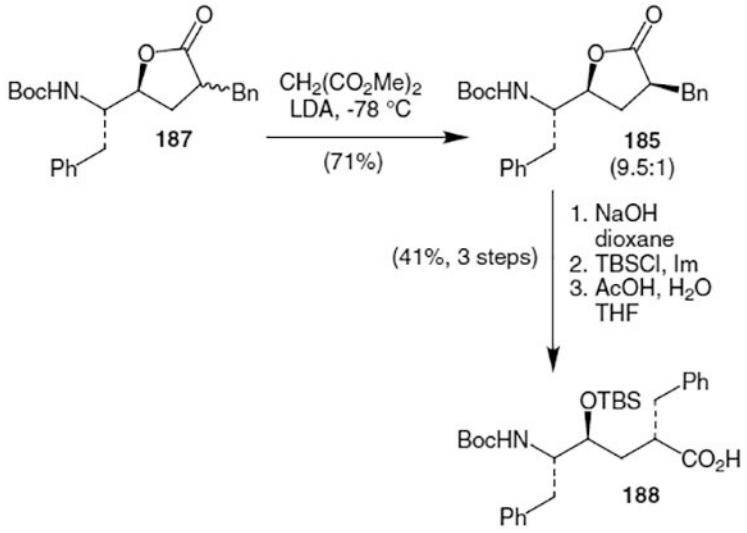

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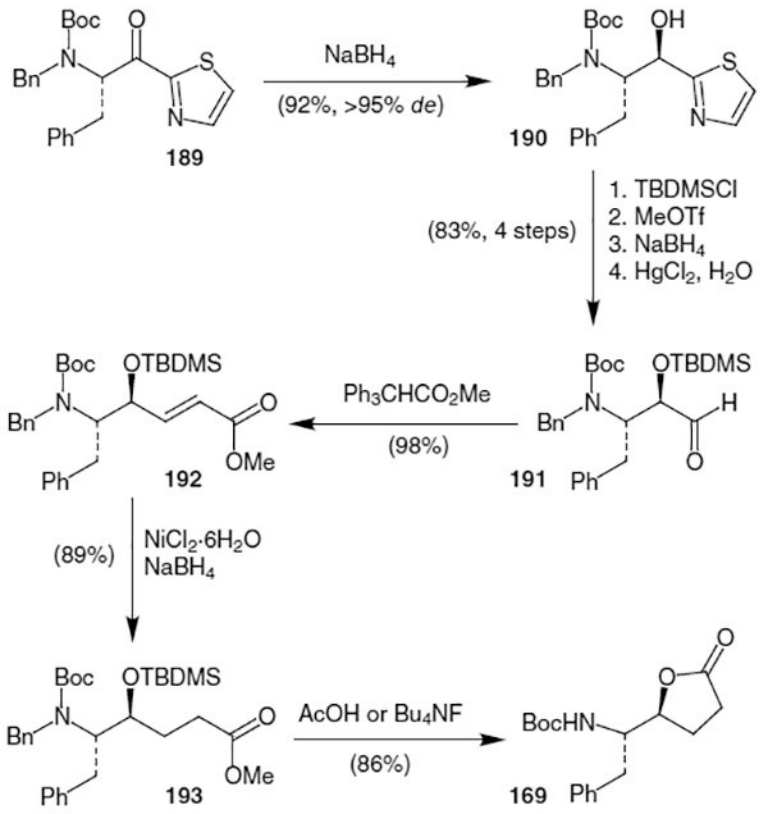

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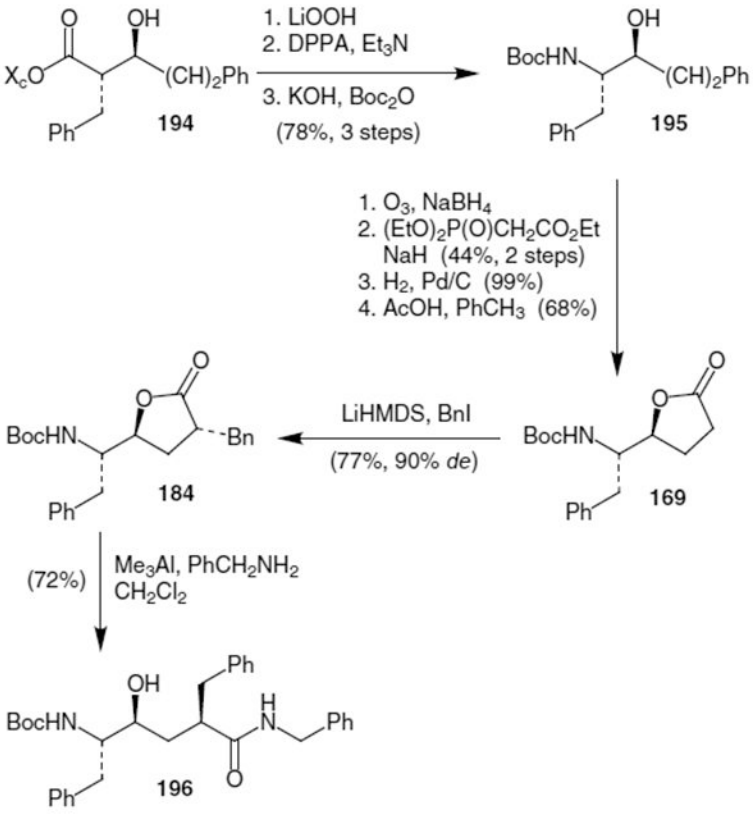

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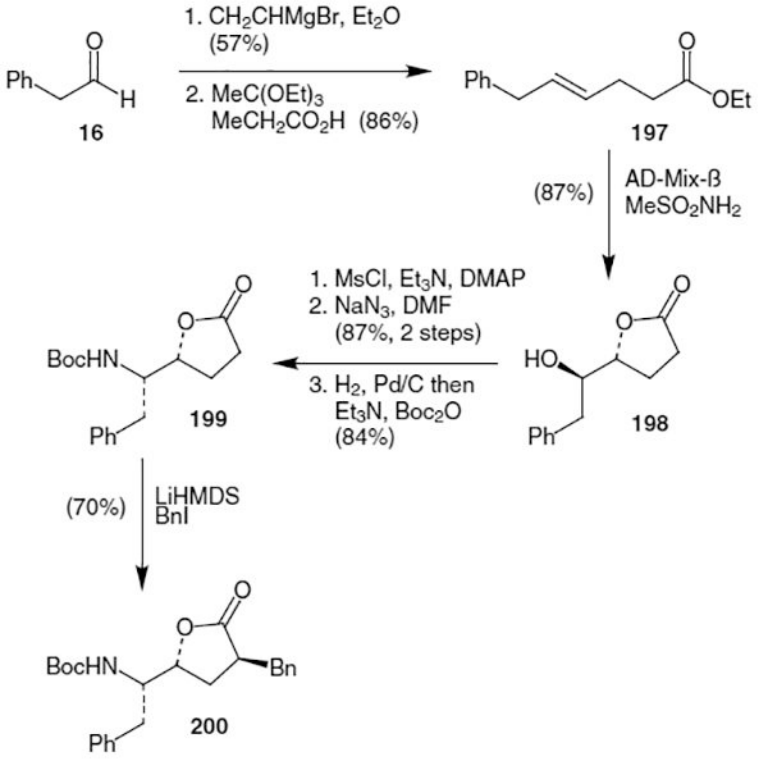

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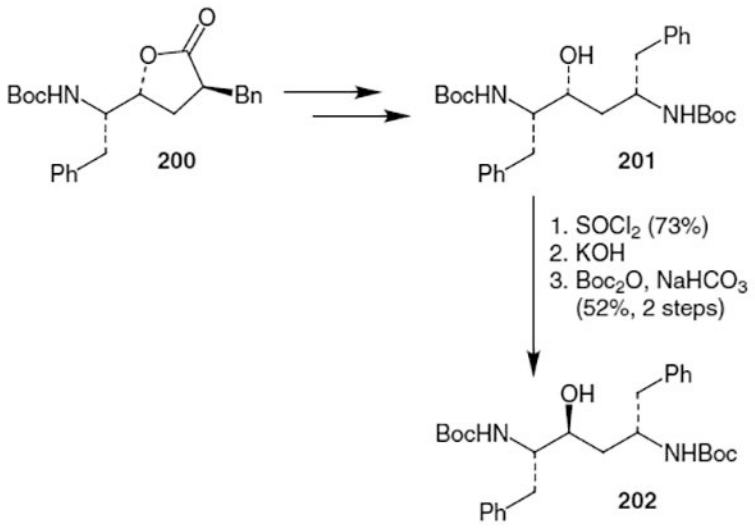

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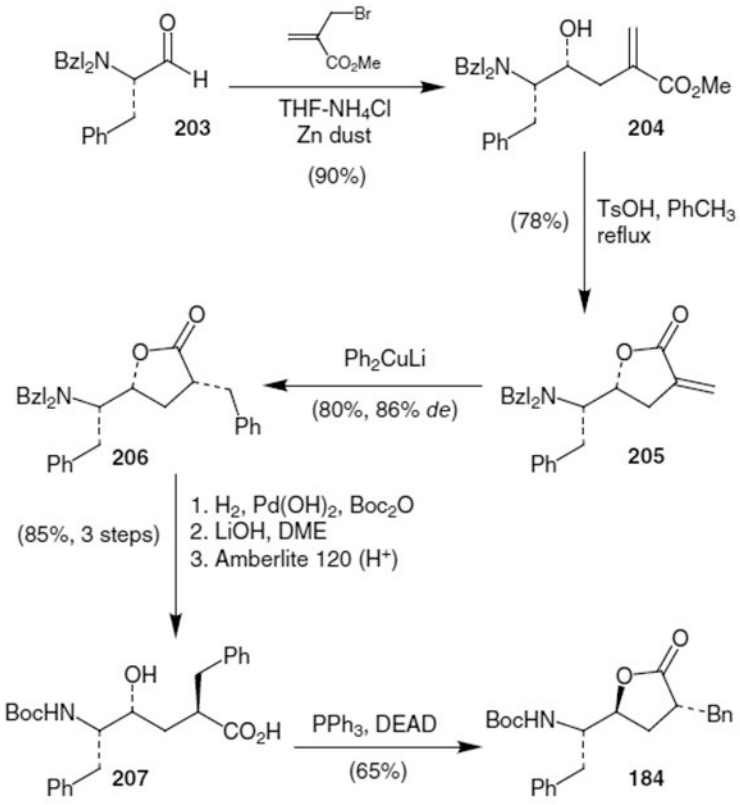

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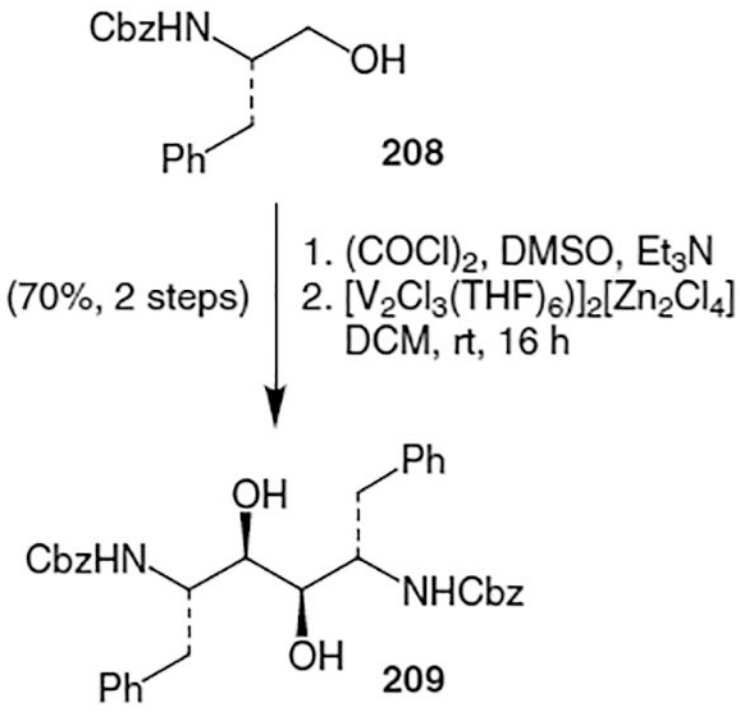

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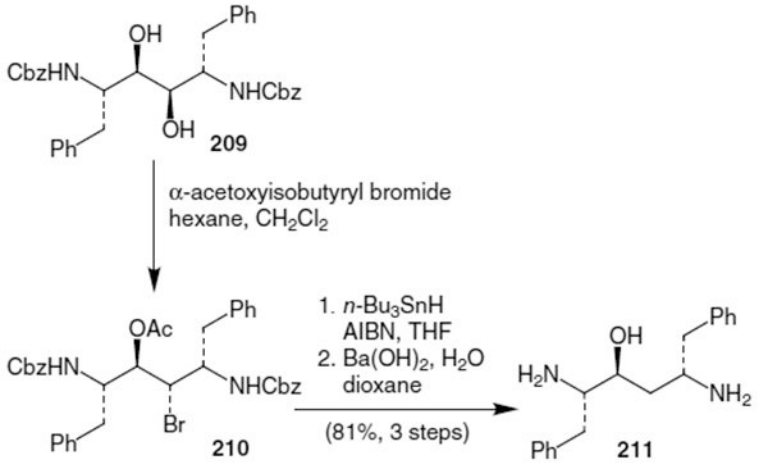

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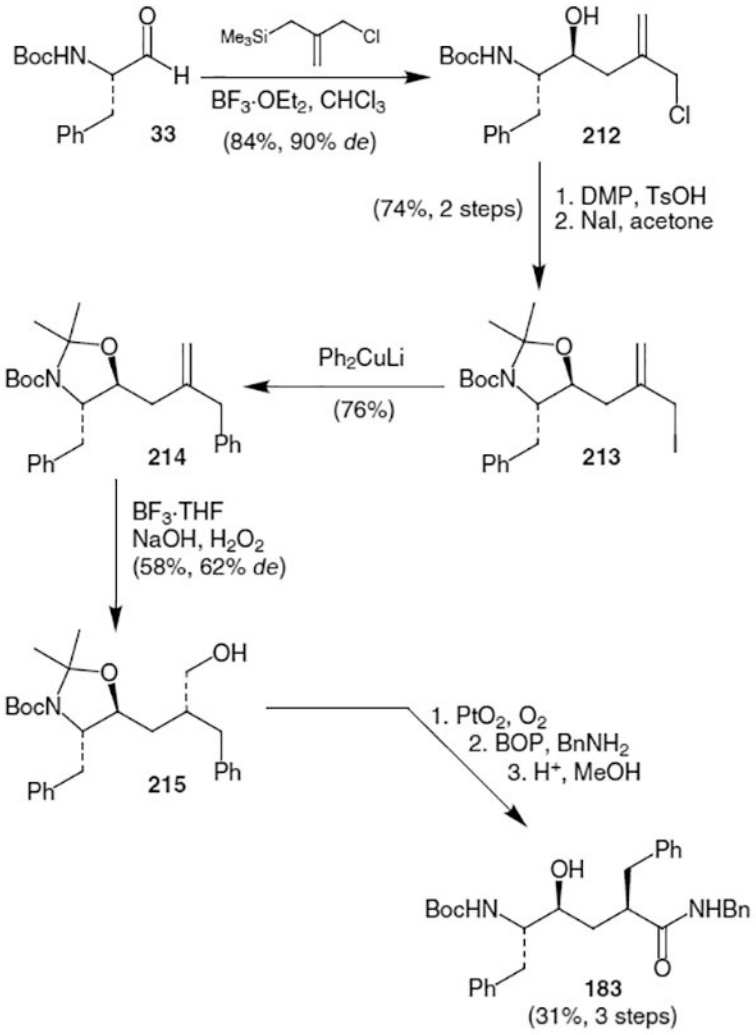

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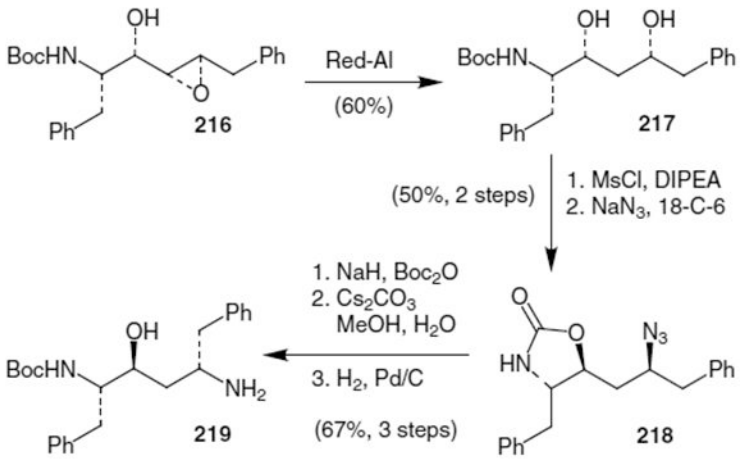

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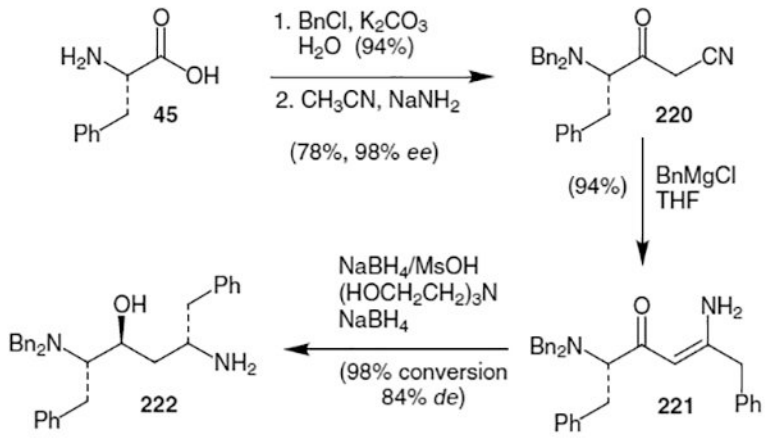

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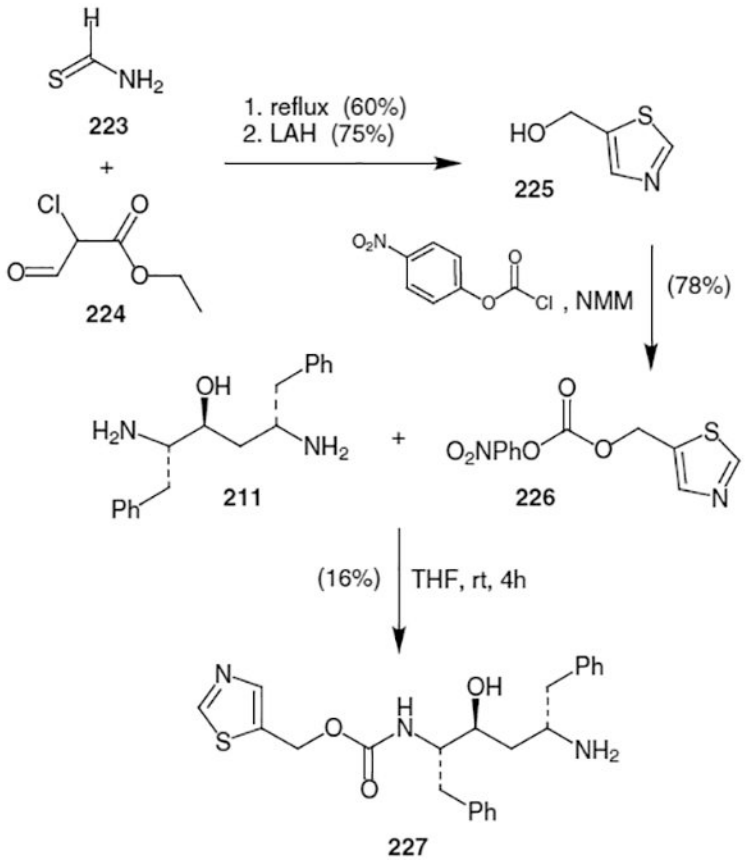

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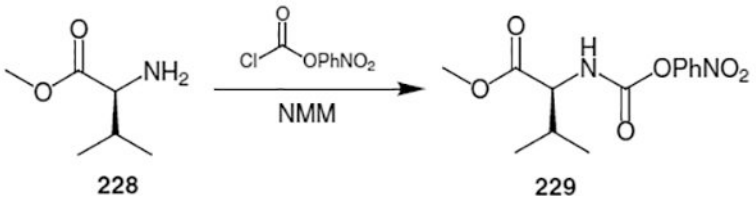

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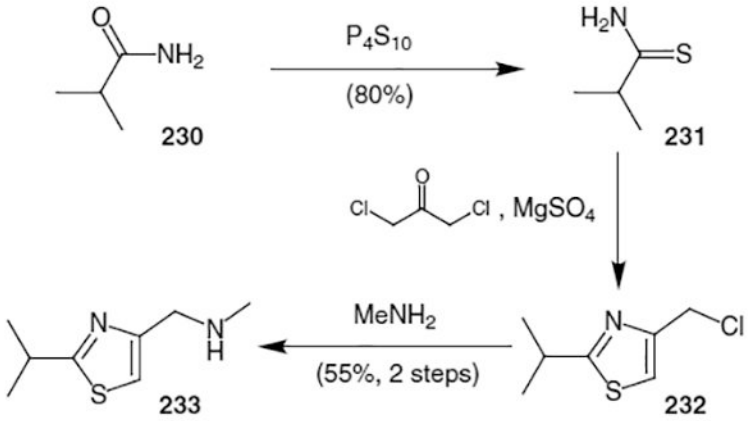
Scheme 59.



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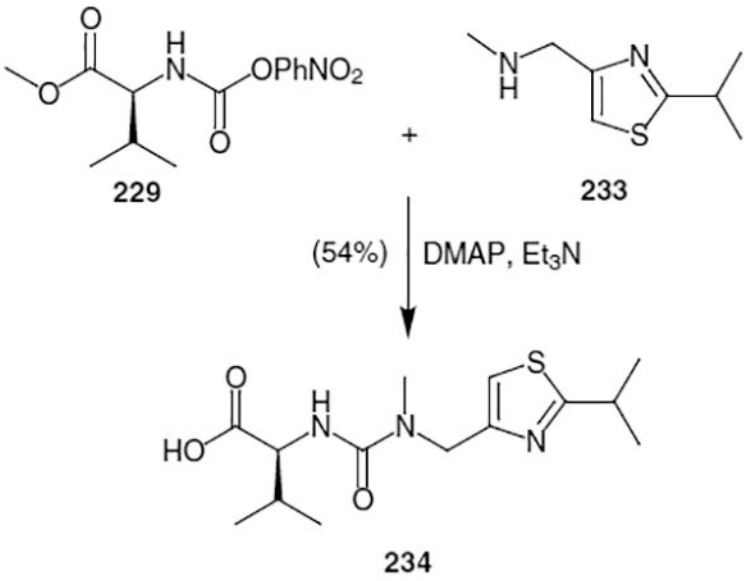

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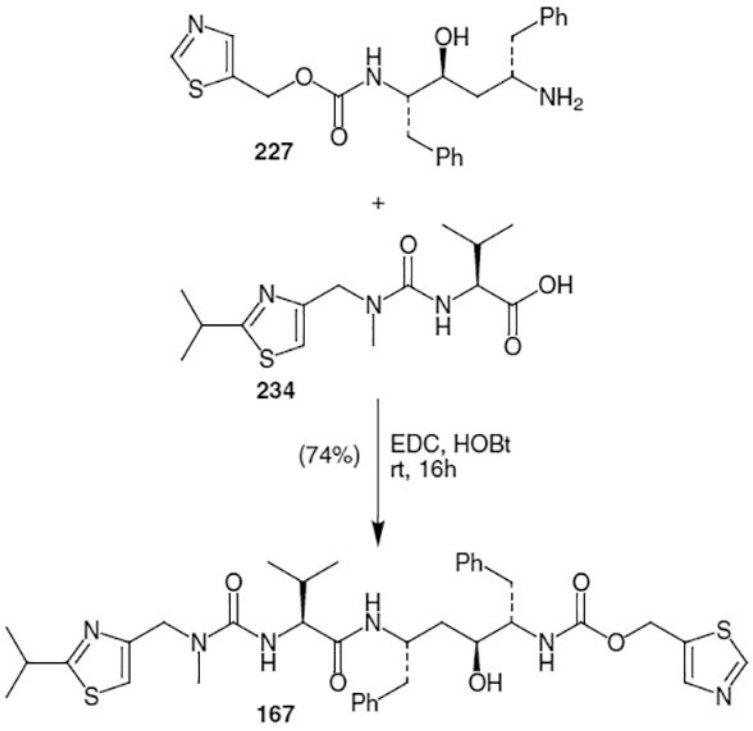

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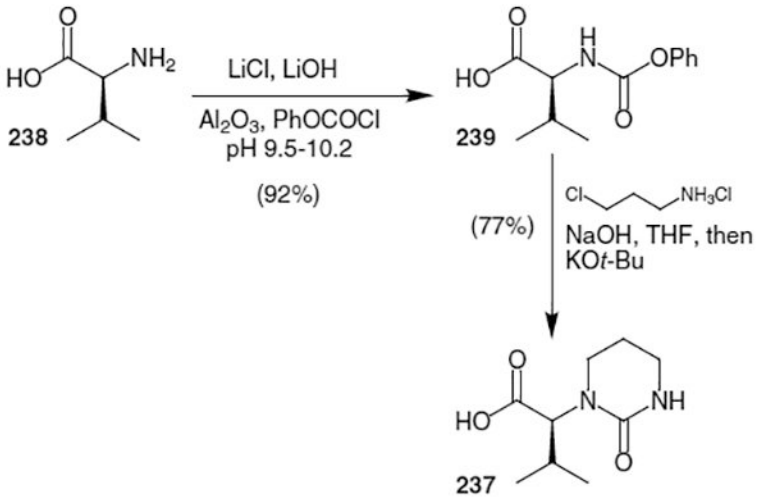

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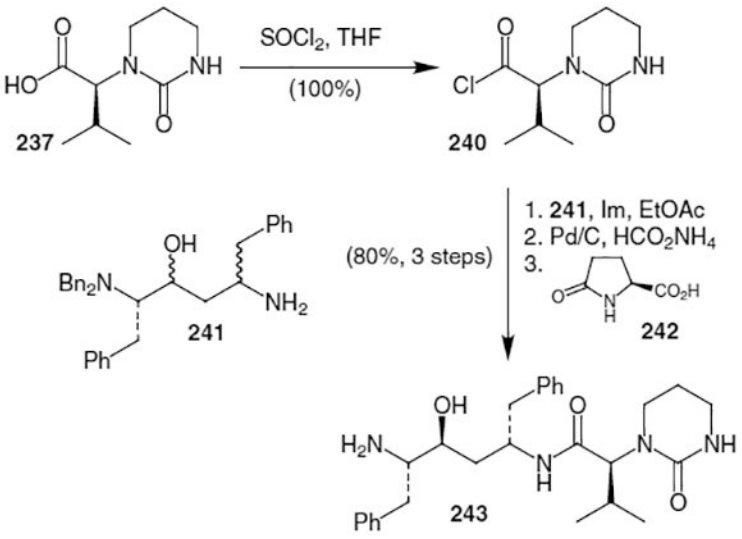

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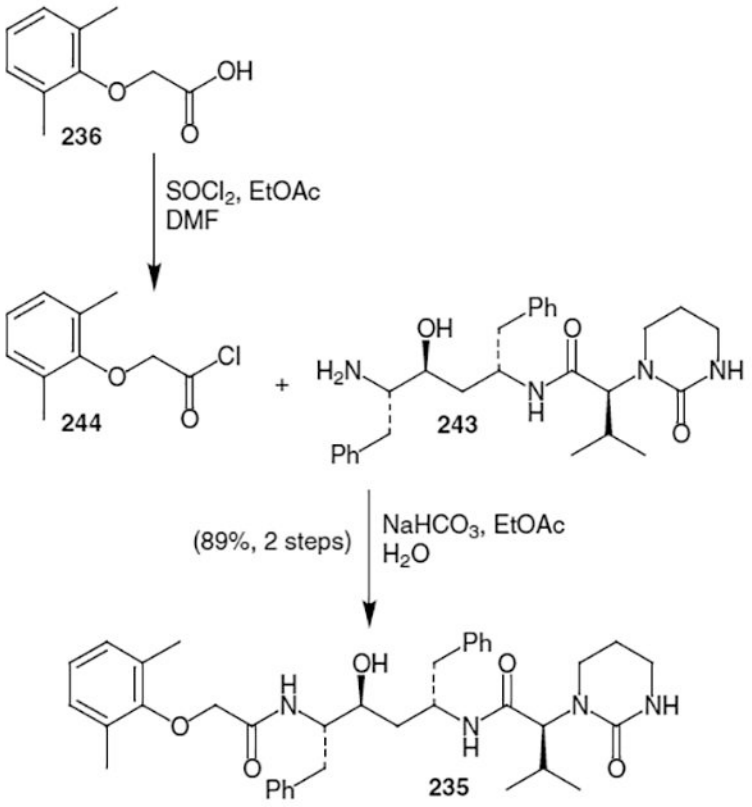

Scheme 65.