Industrial Syntheses of the Central Core Molecules of HIV Protease Inhibitors

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1. Introduction

The recent increase in the number of AIDS patients has become one of the world's greatest social problems. According to the estimation by UNAIDS in 2004,[1] about 40 million people are infected by HIV worldwide—many of whom do not receive therapy because of their economic circumstances. For almost a decade, HIV therapy consisted of a single nucleoside reverse transcriptase inhibitor (NRTI) such as AZT, d4T, or ddI. In the mid 1990s, however, a series of HIV protease inhibitors, which disrupt viral replication, gained approval, and at present, eight such drugs are used in the clinic (Figure 1).[2] The introduction of these drugs in the developed world dramatically reduced the death

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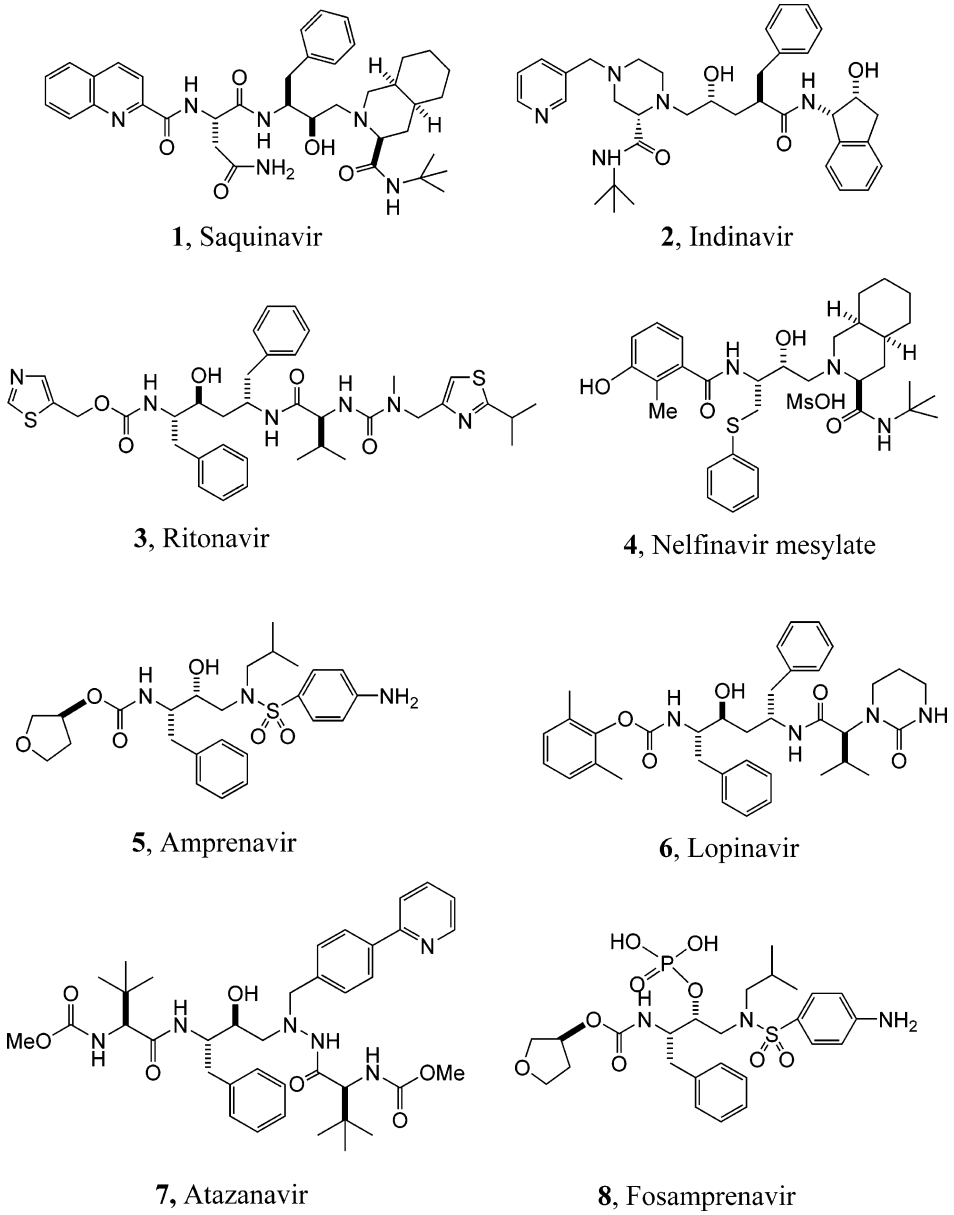


Figure 1. Approved peptidomimetic HIV protease inhibitors.

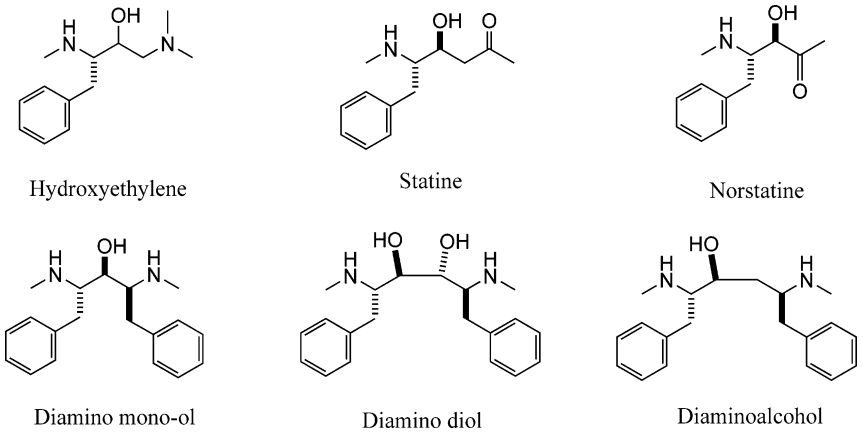


Figure 2. Typical cores of substrate models.

rate from AIDS. As HIV protease, having a C_2-symmetric homodimeric structure, selectively cleaves the Phe-Pro (Tyr-Pro) moiety of the virus polyprotein, the rational design of inhibitors proved possible based on substrate models.[3] Such substrate models consist of hydroxyethylene isosteres, diaminoalcohols, and other related molecules shown in Figure 2—all of which have chiral center(s) at their core.[4] Against this background, we herein review the progress in the synthetic processes required to synthesize the core molecules of the HIV protease inhibitors that have been launched to

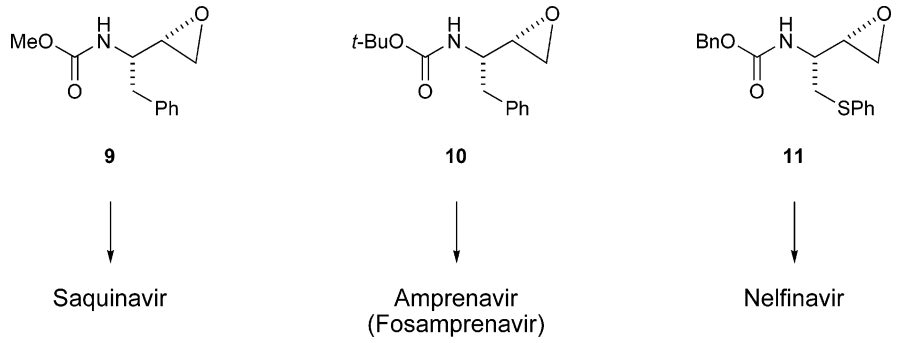
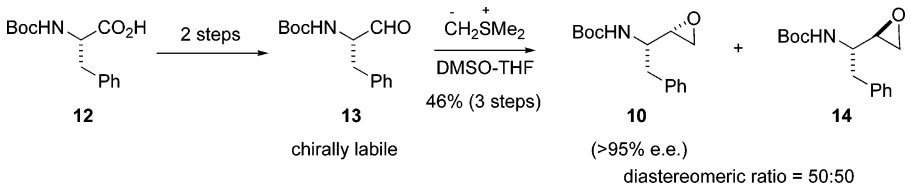
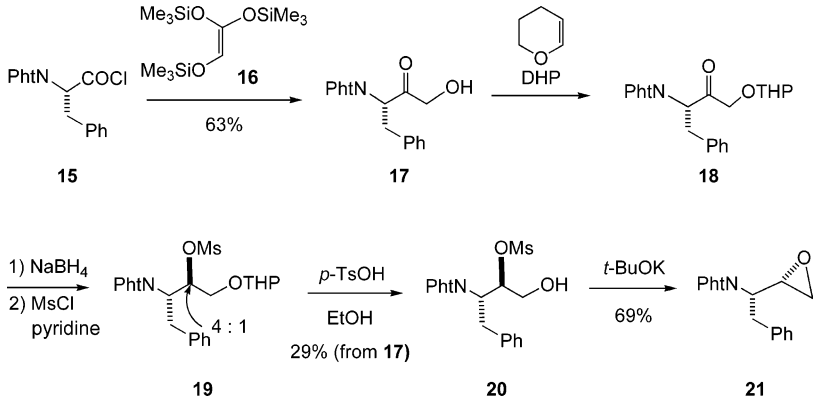


Figure 3. Core *erythro N*-protected aminoepoxides.

Scheme 1



Scheme 2



date, focusing particularly on how to establish the chiral center and the process chemistry involved.

2. Synthesis of erythro N-Protected 3-Amino-1,2-epoxides

Most of the approved HIV protease inhibitors involving hydroxyethylene isosteres—such as Saquinavir (**1**),[5,6] Nelfinavir (**4**),[7] and Amprenavir (**5**)[8] (and its prodrug, Fosamprenavir (**8**)[9])—contain an *erythro* (*anti*-) configuration of an aminoalcohol in the central core, which is derived from the reaction of the corresponding *erythro N*-protected aminoepoxide with an amine. The progress in the syntheses of *erythro N*-protected aminoepoxides described below focuses mainly on the *erythro*-selective reduction of the chloromethyl ketone which is readily available by means of the chloromethylation of the corresponding amino acid.

2.1. Synthesis via Epoxidation with a Sulfur Ylide

The first synthesis of *erythro* (2*S*,3*S*)-*N*-Boc aminoepoxide **10** was reported by Evans *et al.* of Merck in 1985.[10] *N*-Boc-phenylalanine (**12**) was converted to the corresponding aldehyde **13** by reduction followed by oxidation.[11] Since it was found that **13**, being labile, is prone to epimerization, it was further treated without isolation. The key reaction with dimethylsulfonium methylide gave a diastereomeric mixture of **10** and **14** in 46% yield in three steps (Scheme 1). The resulting epoxide **10** was purified by crystallization from petroleum ether followed by recrystallization from hexane. The epoxide **10** was allowed to react with (*R*)-phenethylamine to evaluate the enantiomeric excess, which was confirmed to be more than 95% ee. Although this is not a satisfactory method from the viewpoint of diastereoselectivity and industrial scale manufacture, it is nevertheless noteworthy as the landmark synthesis of *N*-Boc aminoepoxide **10**.

2.2. Synthesis from a Hydroxymethyl Ketone

Parkes *et al.* reported a synthetic process for *erythro N*-phthaloyl aminoepoxide **21** utilizing the hydroxymethyl ketone synthesis method[12] developed by Wissner (Scheme 2).[13] This process was applied in the synthesis of Saquinavir (**1**) in its early development stages. The acid chloride of *N*-phthaloyl phenylalanine (**15**) was allowed to react with tris(trimethylsililoxy)ethene (**16**) to give hydroxymethyl ketone **17** in 63% yield.

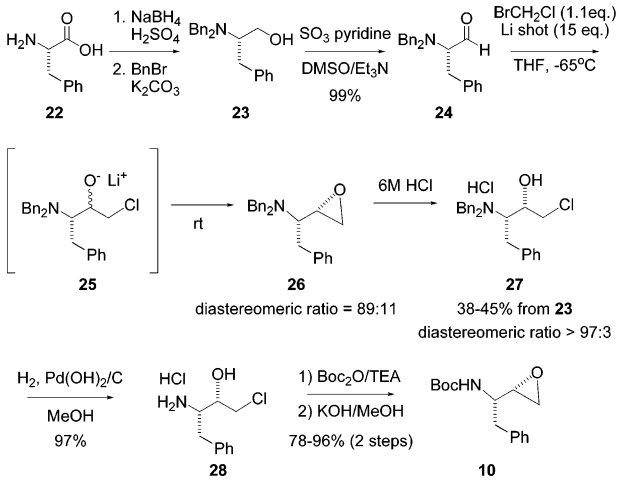
Compound **17** was then protected with DHP followed by reduction with $NaBH_4$. The reduction proceeded with non-chelation control to afford the *threo* aminoalcohol as the major product. After mesylation of the OH group, the mesylate **19** was then converted to *erythro N*-phthaloyl

aminoepoxide **21** by treatment with *p*-toluenesulfonic acid followed by epoxidation with *t*-BuOK in DMF. Although this procedure requires rather lengthy reaction steps and gives the product in low overall yield, it was one of the leading processes in early phase development.

2.3. Synthesis via the *erythro* Selective Chloromethylation of a Phenylalaninal Derivative

Beaulieu *et al.* reported the stereoselective synthesis of the *N*,*N*-dibenzyl-protected aminoepoxide **26**.[14,15] *N*,*N*-Dibenzyl phenylalaninol (**23**) was prepared by the reduction of L-phenylalanine (**22**) with $NaBH_4$ in the presence of H_2SO_4 followed by protection with benzyl bromide. Compound **23** was then oxidized with SO_3-pyridine to give *N*,*N*-dibenzyl phenylalaninal (**24**) in 99% yield. The phenylalaninal **24** was treated with $ClCH_2Li$ prepared *in situ* from $BrCH_2Cl$ with Li metal to give the *erythro N*,*N*-dibenzyl aminoepoxide **26** as a major isomer in a ratio of 89:11 due to the influence of the steric hindrance of the dibenzylamino group. Since the purification of **26** simply by crystallization at this stage was known to be difficult, the product was converted to the aminoalcohol **27** by means of treatment with 6 M HCl without the isolation of the epoxide **26**. The resulting *erythro* aminoalcohol **27** could be purified by crystallization and then derivatized to the *erythro N*-Boc aminoepoxide **10** by hydrogenolysis of the dibenzyl groups followed by Boc protection and subsequent epoxidation under alkaline conditions (Scheme 3). This reaction sequence might be considered as one of the best processes yet developed save for the fact that the chloromethylation requires an excess amount of Li metal and the yield is relatively low.

Scheme 3



Similar procedures for the synthesis of the *erythro N*,*N*-dibenzyl aminoepoxide **26** using this approach have been independently reported by other groups such as Barluenga[16] and Liu.[17]

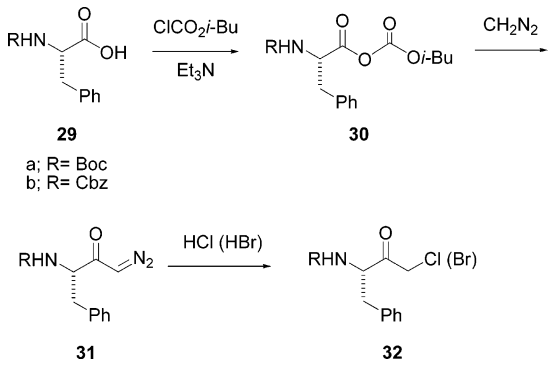
2.4. Synthesis via the *erythro* Selective Reduction of a Halomethyl Ketone

2.4.1. Preparation of Halomethyl Ketones

Halomethyl ketones, prepared by the one carbon elongation of the carboxylate group of an amino acid, are selectively reduced with $NaBH_4$ to give *erythro* aminoalcohols as the major product. As a result, these halomethyl ketones have often been utilized as key intermediates for HIV protease inhibitors.

2.4.1.1. Diazomethane Method. There have been many reports describing the synthesis of halomethyl ketones. One of the easiest ways to obtain halomethyl ketones in the laboratory is the diazomethane method.[18−22] *N*-Alkoxycarbony-protected phenylalanine **29** is first treated with isobutyl chloroformate in the presence of a base to give the mixed anhydride **30** and then treated with diazomethane followed by HCl or HBr treatment to afford the corresponding halomethyl ketone **32** in good yield (Scheme 4). This process is applicable for the synthesis of the Nelfinavir core starting with *S*-phenylcysteine.[7]

Scheme 4



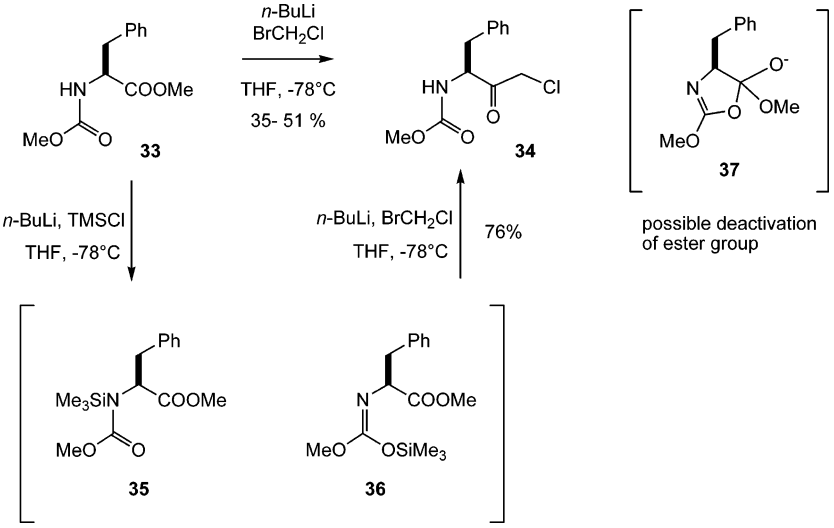
In the past, the performance of such reactions on an industrial scale had been clouded by safety issues due to diazomethane's high toxicity and explosive character.[23] Recently, however, a small number of companies have succeeded in the development of safe industrial scale processes by using a continuous system for diazomethane generation.[24]

2.4.1.2. Chloromethylation of an *N*-Alkoxycarbonyl-Protected Amino Acid Ester. Goehring *et al.* at Hoffmann la Roche developed a direct chloromethylation method for *N*-methoxycarbonyl-phenylalanine methyl ester (**33**) (Scheme 5).[6] The process consisted of the protection of the remaining NH group with TMS followed by chloromethylation with $ClCH_2Li$, prepared *in situ* by the reaction of $BrCH_2Cl$ and BuLi, to give the chloromethyl ketone **34** in 76% yield. When the reaction was carried out without TMS protection, the yield dramatically decreased. Goehring *et al.* postulated that the likely reason for this was intramolecular attack of the carbamate anion to the ester group.

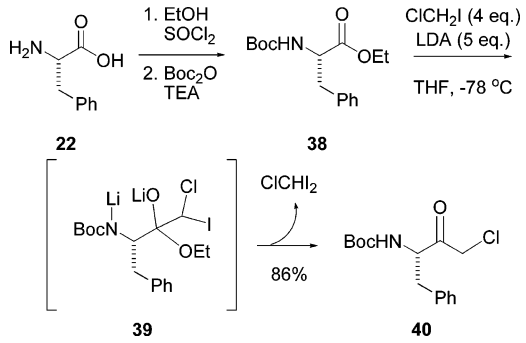
This procedure was also successfully applied to the reaction of the *S*-phenylcysteine derivative used in the synthesis of Nelfinavir.[25] The process seems to be limited only to the synthesis of less sterically hindered *N*-Moc- or *N*-Cbz-protected halomethyl ketones. However, it is a very attractive industrial process owing to the short number of steps.

On the other hand, Chen *et al.* at Bristol-Myers Squibb reported an alternative chloromethylation procedure for *N*-Boc-Phe-OEt **38** (Scheme 6).[26] The ester **38** was treated with 4 equiv of $ClCH_2I$ and 5 equiv of LDA at low temperature to give the chloromethyl ketone **40** in 86% yield. It is assumed that the reaction proceeds via chloroiodomethylation followed by iodine−lithium exchange. Due to the deprotonation of the NH in the carbamate group, the racemization of the amino acid ester might be suppressed. The overall process is very simple and practical, although there are economic considerations in the use of excess amounts of expensive $ClCH_2I$ and LDA.

Scheme 5

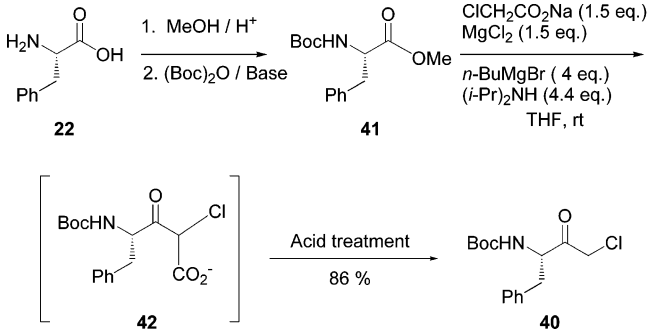


Scheme 6



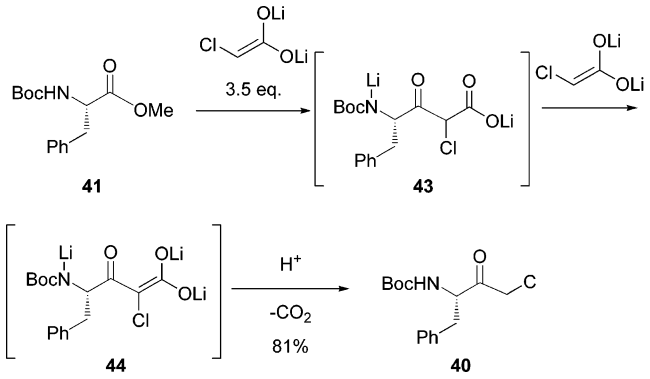
2.4.1.3. Chloromethylation via a β-Keto Acid or Ester. Nishiyama *et al.* at Kaneka developed an excellent process to produce the chloromethyl ketone **40** starting with *N*-Boc-Phe-OMe **41**.[27] The methyl ester **41** was allowed to react with sodium chloroacetate and *n*-BuMgBr (4 equiv)/ *i*-Pr_2NH (4.4 equiv) in the presence of $MgCl_2$ followed by acid treatment directly affording the desired chloromethyl ketone **40** with spontaneous decarboxylation in good yield (Scheme 7). One advantage of this process was that the reaction did not require a low-temperature reactor. This process also was reported to be applicable to the synthesis of Nelfinavir.[27]

Scheme 7



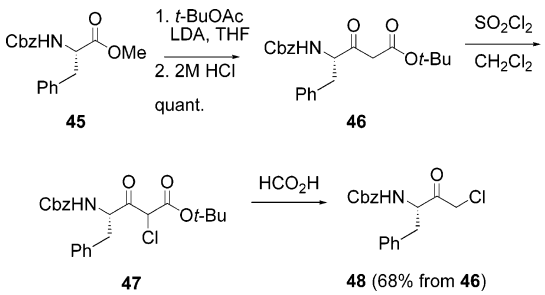
Independently, a similar reaction of **41** with a dianion of chloroacetate was reported to give the chloromethyl ketone **40** by Wang *et al.* (Scheme 8).[28] In this case, a low-temperature reactor is necessary to prepare the dianion with *n*-BuLi at −78 °C.

Scheme 8

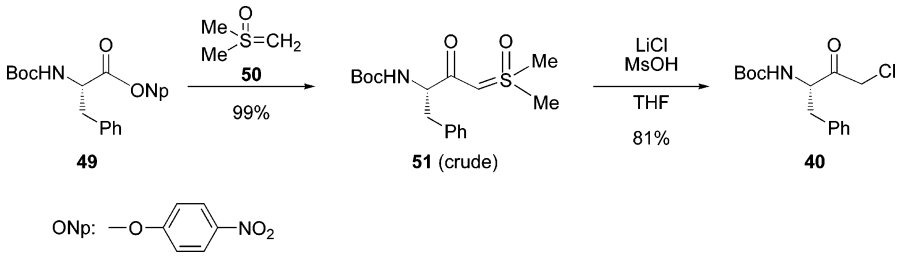


We have found that the cross Claisen condensation of *N*-Cbz-phenylalanine methyl ester **45** with the Li enolate of *tert*-butyl acetate takes place very efficiently to give the ketoester **46** in almost quantitative yield without forming a *tert*-alcohol by further attack of the enolate.[29] It is worth noting that an activated ester such as imidazolide should normally be used in this reaction in order to avoid side reactions.[30,31] The ketoeter **46** can be converted to the chloromethyl ketone **48** by chlorination with SO_2Cl_2 and subsequent deprotective decarboxylation of the *tert*-butyl ester (Scheme 9).[32−34] However, the process has a limitation in that it is only applicable to an *N*-Cbz-protected substrate.

Scheme 9



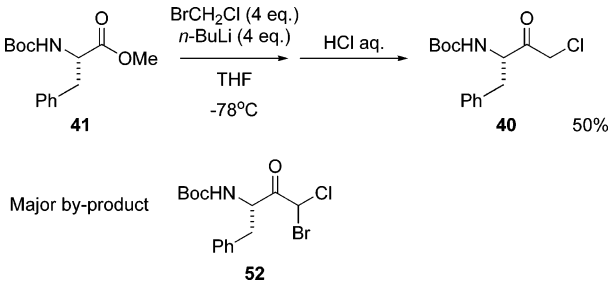
Scheme 10



2.4.1.4. Chloromethylation via a Sulfur Ylide. Wang *et al.* reported an alternative synthetic process for the chloromethyl ketone **40** (Scheme 10).[23] *N*-Boc-phenylalanine *p*-nitrophenyl ester (**49**) was treated with dimethylsulfoxonium methylide (**50**), prepared from trimethylsulfoxonium iodide and *t*-BuOK, to give the *β*-keto sulfur ylide **51** in good yield with high enantiomeric excess. The ylide was then converted to the desired chloromethyl ketone **40** by treatment with LiCl and MsOH in THF in 81% yield. It is most interesting to note that they observed complete racemization using the methyl ester instead of the *p*-nitrophenyl ester.

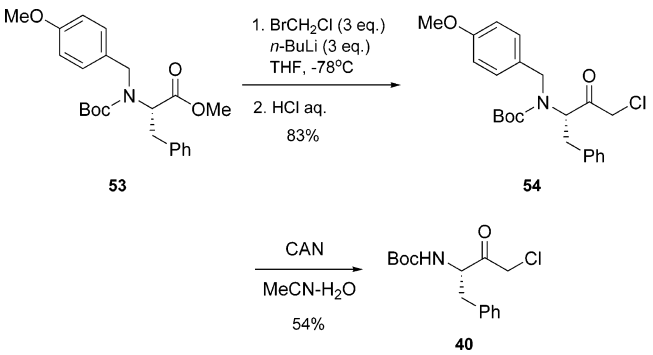
2.4.1.5. Chloromethylation via an Oxazolidinone. As reported previously by Barluenga *et al.*,[16] the direct chloromethylation of *N*,*N*-dibenzyl phenylalanine ester proceeds smoothly to give the chloromethyl ketone in good yield. In the case of the *N*-Moc-protected phenylalanine ester, chloromethylation proceeds well after the protection of the remaining NH with a TMS group.[6] To establish a still more efficient approach for the synthesis of the chloromethyl ketone, we investigated the reaction of *N*-Boc-Phe-OMe **41** with $ClCH_2Li$ *in situ* prepared from $BrCH_2Cl$ and *n*-BuLi (Scheme 11). The best yield we obtained was 50% along with various byproducts such as bromochloromethyl ketone **52** when we used an excess amount of *n*-BuLi (4 equiv) and $BrCH_2Cl$ (4 equiv), suggesting that NH protection is necessary to obtain good results. Therefore, we also attempted the protection of the methyl ester **41** with TMSCl, but we did not obtain good results probably due to the steric hindrance of the *tert*-butyl group.

Scheme 11



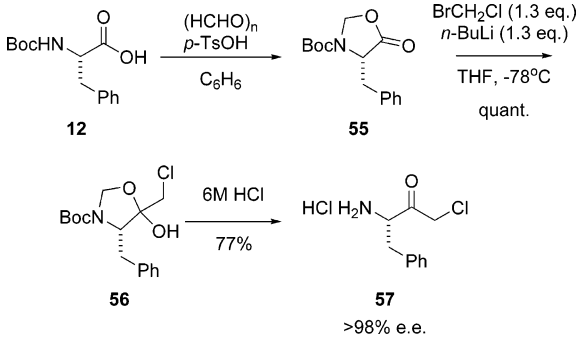
Next, to determine whether chloromethylation could proceed in good yield if the carbamate NH was protected with an appropriate protecting group, we turned our attention to the utilization of a *p*-methoxybenzyl (PMB) group for the protection of NH. As we anticipated, the chloromethylation of **53** proceeded nicely to give the chloromethyl ketone **54** in 83% yield after workup. Unfortunately, however, the deprotection of PMB with cerium(IV) ammonium nitrate (CAN) resulted in a moderate yield of the desired chloromethyl ketone **40** (Scheme 12).

Scheme 12



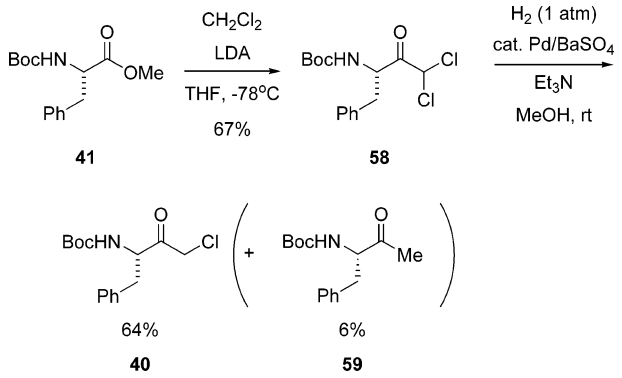
Encouraged by the above findings, we next attempted the chloromethylation of the *N*-Boc-protected 3-oxazolidin-5-one **55**,[35] which can be prepared very easily by the reaction of *N*-Boc-Phe **12** with paraformaldehyde in the presence of an acid catalyst. The reaction proceeded very nicely to give 5-chloromethyl-5-hydroxy-3-oxazolidine **56** in quantitative yield even with 1.3 equiv of *n*-BuLi. Compound **56** was then successfully converted to the unprotected chloromethyl ketone **57** as a HCl salt by hydrolysis in 77% yield without racemization (Scheme 13).[36] One drawback of this process may be that loss of the Boc group during hydrolysis is inevitable. On the other hand, the reaction can be applicable to *N*-Cbz-protected phenylalanine derivatives and *N*-Cbz-protected chloromethyl ketone is obtainable after hydrolysis with an acid catalyst such as amberlyst.

Scheme 13



2.4.1.6. Chloromethylation via a Dichloromethyl Ketone. After the successful chloromethylation of an oxazolidinone derivative, we became interested in the dichloromethylation of *N*-Boc-Phe-OMe **41**, since Cl_2CHLi is considered to be more stable than $ClCH_2Li$.[37] As we expected, dichloromethylation duly afforded the ketone **58** in 79% yield (67% isolated) with 2.3 equiv of LDA at −78 °C (Scheme 14);[38] the reaction could be performed even at −20 °C, though the yield was slightly lower. The dichlo-

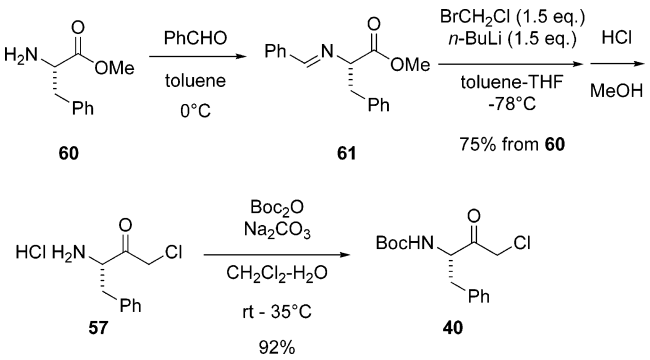
Scheme 14



romethyl ketone **58** thus obtained was subjected to catalytic hydrogenation using Pd/C to obtain the chloromethyl ketone **40** in 66% yield. However, prolonging the reaction time caused cleavage of the Boc group due to HCl generation. From the point of view of reproducibility, it is therefore preferable to carry out hydrogenolysis with $Pd/BaSO_4$ (Lindlar catalyst) in the presence of triethylamine.

2.4.1.7. Chloromethylation via an *N*-Benzylidene Phenylalanine Ester. We further investigated the chloromethylation process by attempting to decrease the amount of lithium; this eventually led to the development of a novel industrial process. First, we attempted the chloromethylation of *N*-benzylidene-protected phenylalanine methyl ester **61** using 1.3 equiv of $BrCH_2Cl$ and 1.3 equiv of *n*-BuLi. After quenching the reaction mixture at low temperature, we were delighted to find that the reaction proceeded very nicely to give the chloromethyl ketone **57** as a hydrochloride salt in 75% yield without any racemization or other side reactions. The hydrochloride salt **57** was easily isolated by crystallization from MeOH/MTBE. The acid-free form of this salt is quite labile so that it was difficult to optimize the conditions for Boc protection. However, this could be overcome by the addition of **57** to a mixture of a dichloromethane solution of Boc_2O and an aqueous $NaHCO_3$ solution with vigorous stirring (Scheme 15).[39]

Scheme 15



By applying this process on an industrial scale, we confirmed its scalability to 6000 L giving the desired chloromethyl ketone **40** with good purity in high yield. An advantage of this process is that it requires only a small excess amount of *n*-BuLi.

2.4.2. erythro Selective Reduction of Halomethyl Ketones

N-Alkoxycarbonyl α-aminoalkyl α′-halomethyl ketones may be selectively reduced with several agents such as $NaBH_4$ to give *erythro* aminoalcohols. Since halomethyl ketones can be prepared efficiently by a variety of methods as described above, such a reduction is one of the most useful means of synthesizing *erythro N*-protected aminoepoxides (Scheme 16). Extensive studies on the improvement of diastereoselectivity have been carried out by many groups. Typical examples of the reduction of *N*-Boc chloromethyl ketone **40** and *N*-Moc chloromethyl ketone **34** are summarized in Tables 1 and 2.

It has long been known that chloromethyl ketones can be reduced with $NaBH_4$ to give *erythro* aminoalcohols.[44] Chen *et al.* reported that the diastereoselectivity of $NaBH_4$ reduction was improved to 9:1 by using EtOH as solvent and elevating the reaction temperature to 0 °C from −78 °C.[26]

Goehring *et al.* reported that the Meerwein−Pondorf−Verley (MPV) reduction of *N*-Moc chloromethyl ketone **34** with $Al(Oi\text{-}Pr)_3$ at 50 °C gave the corresponding *erythro* aminoalcohol **62** in a diastereomeric ratio of 95:5.[6] After crystallization, the alcohol **62** was obtained in 89% yield. Applying a method similar to that for the *N*-Boc chloromethyl ketone **40**, Malik *et al.* observed that the aminoalcohol **63** was afforded in a diastereomeric ratio of 96.9:3.1 although it required a rather longer reaction time of 96 h.[42] To accelerate this reaction, it is necessary to eliminate acetone generated during the reduction. However, MPV reduction is one of the best methods to produce *erythro* aminoalcohols from halomethyl ketones. There are several reported methods to accelerate the reaction without eliminating acetone which involve $LiAl(Ot\text{-}Bu)_3H$/EtOH,[45] $i\text{-}Bu_2AlH$/ROH,[40] $i\text{-}Bu_3Al$/*i*-PrOH/MsOH,[41] and $Al(Oi\text{-}Pr)_3$/*i*-PrOH/MsOH.[46] All of these reaction systems are considered to proceed according to the MPV reduction mechanism. The MPV reduction could also be applied to the reduction of the *S*-phenylcysteine derivative to give the corresponding *erythro* aminoalcohol with high diastereoselectivity, 95:5.[40,41,46]

Patel *et al.* reported that the enzymatic reduction of **40** gave the alcohol **63** in 80% yield with excellent *erythro* selectivity.[47,48] However, this method seems inefficient in terms of productivity because of the low concentration of the enzymatic reaction.[47] Recently, we succeeded in carrying out a highly *erythro*-selective reduction of the chloromethyl ketone **40** via asymmetric transfer hydrogenation with HCO_2H/Et_3N catalyzed by Cp*RhCl[(*S*,*S*)-Tsdpen] giving a 90:10 ratio of the product.[49]

Since the *erythro* aminoalcohols thus obtained have lower solubility than the corresponding *threo* isomers in various solvents, the diastereomeric ratio of the products can be easily improved by recrystallization.[26] Therefore, a highly pure *erythro N*-protected aminoepoxide such as **9**, **10**, or **11**

Scheme 16

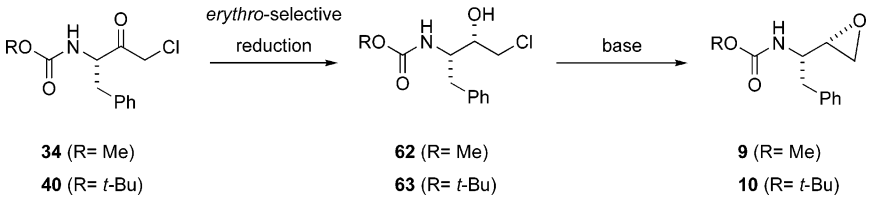


Table 1. *erythro* Selective Reduction of *N*-Boc Chloromethyl Ketone 40

reagents	solvents	temp (°C)	time (h)	yield (%)	selectivity *erythro*	selectivity *threo*	ref
i-Bu_2AlH, Ph_2CHOH	toluene	rt	2	100	99.1	0.9	40
i-Bu_3Al, *i*-PrOH, MsOH	hexane/toluene	25	16	98.6	98.2	1.8	41
i-Bu_2AlH, *i*-PrOH, MsOH	toluene	25	16	97.3	98.0	2.0	41
i-Bu_2AlH, *i*-PrOH	toluene	rt	2	94.7	97.7	2.3	40
Al(O-*i*-Pr)$_3$	*i*-PrOH	50	96	98.1	96.9	3.1	42
$NaBH_4$	EtOH	−78−0	12	76	90.0	10.0	26
$NaBH_4$	CH_2Cl_2/MeOH	0	1	83	83.2	16.8	43
$NaBH_4$, $CeCl_3 \cdot 7H_2O$	THF	rt	5	96	62.5	37.5	42
$NaBH_3CN$, AcOH	THF	rt	2	95	59.0	41.0	42

Table 2. *erythro* Selective Reduction of *N*-Moc Chloromethyl Ketone 34

reagents	solvents	temp (°C)	time (h)	yield (%)	selectivity *erythro*	selectivity *threo*	ref
i-Bu_2AlH, *i*-PrOH	toluene	rt	2	85.3	96.7	3.3	40
Al(O*i*-Pr)$_3$, *i*-PrOH, MsOH	toluene	40	1.5	89.9	96.5	3.5	46
i-Bu_3Al, *i*-PrOH, MsOH	hexane/toluene/THF	25	16	97.1	96.4	3.6	41
LiAl(O*t*-Bu)$_3$H, EtOH	EtOH	−15		90[a]	95.0	5.0	45
Al(O*i*-Pr)$_3$	*i*-PrOH	50		89[a]	95.0	5.0	6
$NaBH_4$	MeOH	−15	1.5	62[a]	75.0	25.0	45

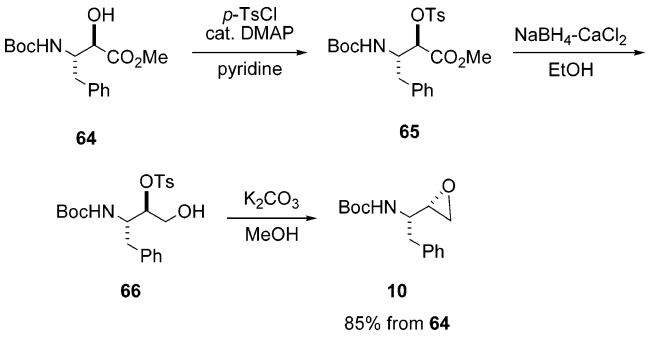
[a] Yield after crystallization.

(Figure 3) can be easily prepared by epoxidation after removing the isomer at the aminoalcohol stage.

2.5. Other Miscellaneous Methods

Scientists at Nippon-Kayaku reported that *threo* β-amino-α-hydroxycarboxylic acid methyl ester **64** could be transformed easily into the *erythro N*-Boc aminoepoxide **10** by tosylation and $NaBH_4$ reduction in EtOH. This was followed by epoxidation with inversion of the configuration at the 2-position under alkaline conditions (Scheme 17).[50]

Scheme 17

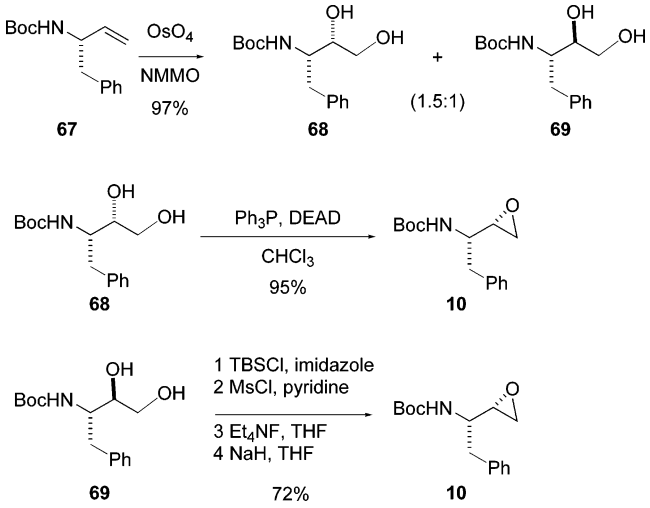


Since compound **64** is a common intermediate of both *erythro N*-Boc aminoepoxide **10** and *threo N*-Boc aminoepoxide **14**, its synthesis will be described in section 3.1.

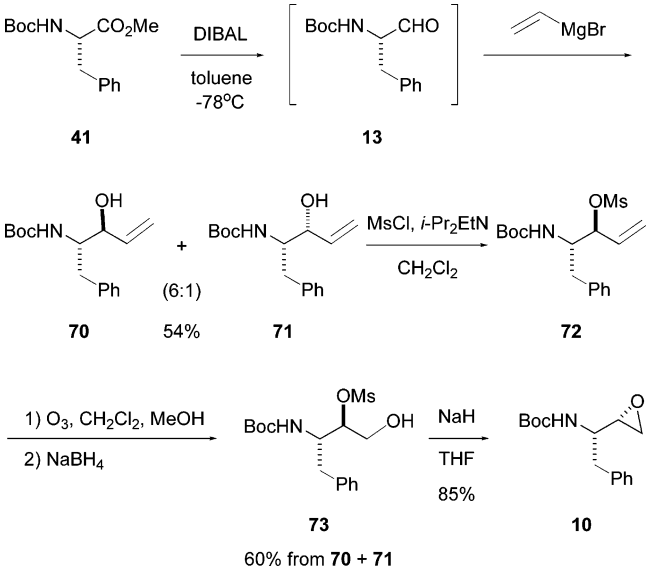
Branalt *et al.* reported that the *N*-Boc amino-diols **68** and **69** could be obtained by dihydroxylation of the olefin **67** (Scheme 18).[51]

N-Boc-3-amino-4-phenylbutene (**67**) was prepared from Boc-Phe-OMe **41** by DIBAL reduction and a subsequent Wittig reaction.[52] Compound **67** was treated with OsO_4/NMMO to give the amino-diols **68** and **69** in a diastereomeric ratio of 1.5:1. The diols **68** and **69** could be separated by fractional crystallization from toluene. It is interesting to note that the epoxidation of the same olefin **67** was reported to give the *threo* isomer as a major product (*vide infra*). The author, however, noted that both isomers of the diols can be transformed into the *erythro N*-Boc aminoepoxide **10**. The *erythro* amino-diol **68** was converted to **10** in 95% yield by

Scheme 18

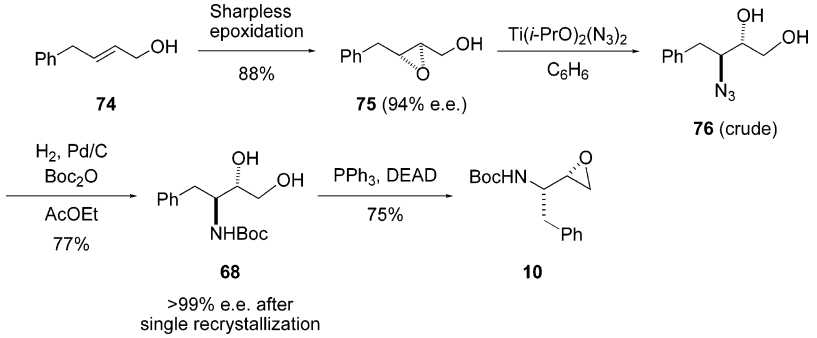


Scheme 19



treatment with Mitsunobu reagent. On the other hand, the *threo* amino-diol **69** was also derivatized to the *erythro*

Scheme 20



N-Boc aminoepoxide **10** by the following reaction sequence: (1) protection with TBSCl at the primary position; (2) mesylation of the secondary alcohol; (3) deprotection of the primary alcohol with a fluoride anion; and (4) epoxidation with NaH. The overall yield for these four steps was 72%.

Another concise synthesis of compound **10** has been reported by Green *et al*. of Abbott (Scheme 19).[53] *N*-Boc-L-phenylalanine methyl ester (**41**) was treated with *i*-Bu_2-AlH at low temperature to give the aldehyde **13**. Interestingly, they have found that *in situ* addition of excess vinylmagnesium bromide provided a 6:1 mixture of allylic alcohol **70** and **71** in 54% yield, although it has been reported that the isolated aldehyde **13** gave the almost 1:1 mixture of the product.[54] Compound **70** was then converted to the mesylate **72** followed by ozonolysis and *in situ* reduction with $NaBH_4$ to provide alcohol **73**, which was eventually transformed into the *erythro N*-Boc aminoepoxide **10**.

Catasus *et al.* have reported the synthesis of **10** from the *erythro* amino-diol **68** derived via Sharpless asymmetric epoxidation and ring opening by azide, followed by reduction and Boc protection (Scheme 20).[55] The *erythro* amino-diol **68** thus obtained having high optical purity (>99% ee) was then converted to the *erythro N*-Boc aminoepoxide **10** under Mitsunobu conditions.

There have been several other reports of the synthesis of *erythro N*-protected 3-amino-1,2-epoxides starting from chiral building blocks such as a chiral aminoindanol,[56,57] a chiral seven-membered ring aminoalcohol,[58] D-tartaric acid,[59] (3*S*)-hydroxy-γ-butyrolactone,[60] and L-mannonic γ-lactone.[61] However, these methods require rather lengthy reaction steps to be performed on an industrial scale, although the methodologies do offer a number of interesting insights from a scientific point of view.

3. Synthesis of threo N-Protected 3-Amino-1,2-epoxides

Investigations into protease inhibitors containing *threo* (*syn*-) aminoalcohols were also undertaken by several groups for more than a decade, and eventually Atazanavir, which has a *threo* aminoalcohol as the central core, was approved by the FDA in 2003.[62,63] In this section, we describe the major industrial procedures for the synthesis of *threo*

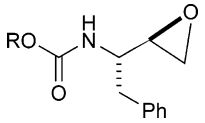
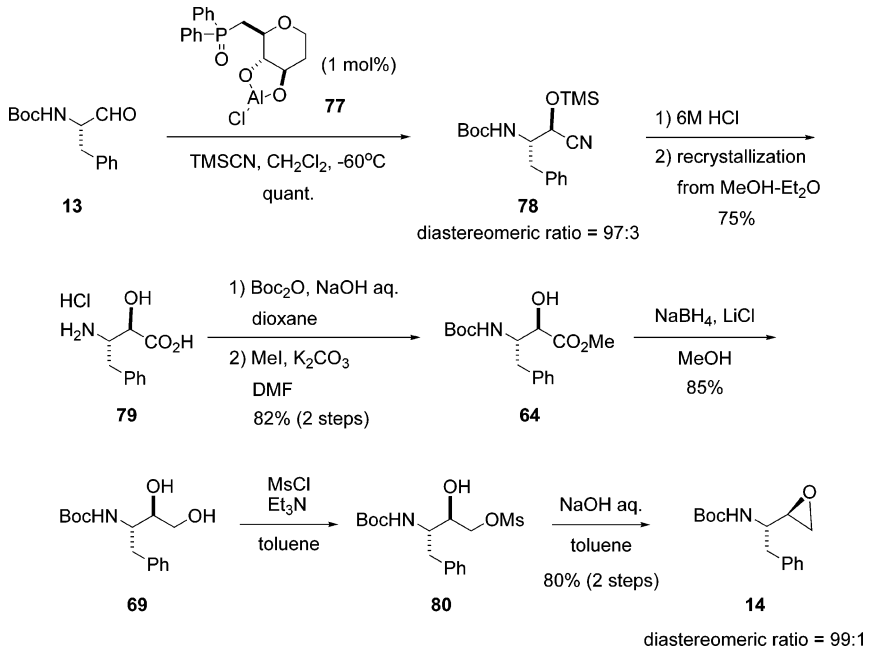


Figure 4. Core *threo* (2*R*,3*S*)-aminoepoxide.

N-protected 3-amino-1,2-epoxides (Figure 4) leading to Atazanavir (**7**).

Scheme 21

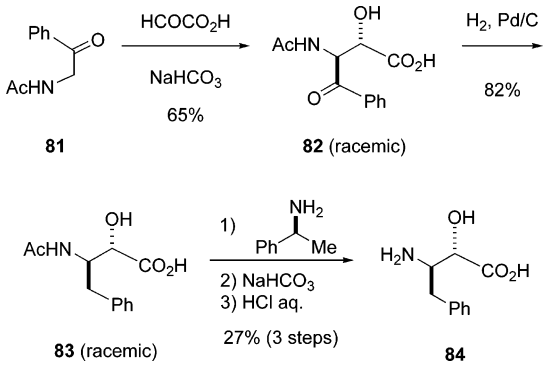


3.1. Synthesis from *threo N*-Protected 3-Amino-4-phenylbutan-1,2-diol

Nogami *et al.* reported the synthesis of the *threo* amino-diol **69** using bifunctional catalyst **77**.[64] The catalytic diastereoselective cyanosilylation of *N*-Boc-phenylalaninal (**13**) in the presence of **77** afforded the *threo* isomer **78** as a major isomer in a ratio of 97:3. Acid hydrolysis of the cyanide **78** with 6 M HCl followed by recrystallization from MeOH/Et_2O gave the diastereomerically pure *threo* (2*R*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid (**79**, *threo*-AHPBA) as a HCl salt. The acid **79** was then converted to *threo N*-Boc-AHPBA methyl ester **64** by conventional means. The ester **64** was reduced with $NaBH_4$/LiCl to give the *threo N*-Boc amino-diol **69** in 85% yield. Compound **69** was then selectively mesylated at the primary alcohol and subsequently treated with NaOH to give the *threo N*-Boc-aminoepoxide **14** in 80% (Scheme 21).[64] Independently, a similar procedure for the synthesis of **14** from *threo N*-Boc-AHPBA methyl ester **64** was reported by Sagawa *et al.* at Nippon-Kayaku in 1999.[65]

It is worth noting that the synthesis of *threo*-AHPBA has been studied for a long time since the discovery of *threo*-(2*S*,3*R*)-AHPBA (**84**) as an enzyme inhibitor in the natural product by Umezawa *et al.*[66−68] One of the earlier excellent approaches to this compound is the aldol reaction of glyoxilic acid and α-acetylamino acetophenone **81** followed by the reduction of ketone **82** and optical resolution (Scheme 22).[69]

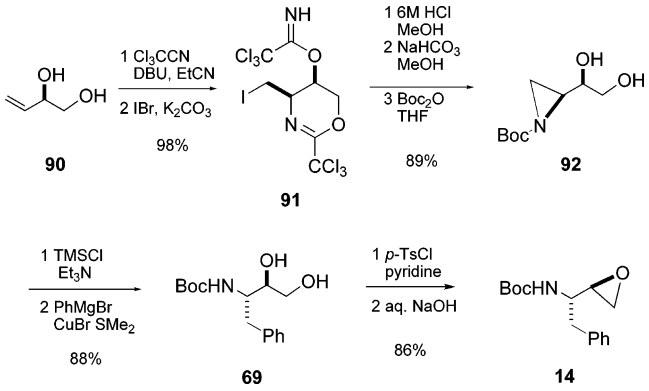
Scheme 22



Ojima *et al.* reported a unique approach to the *threo*-AHPBA derivative **89**, which was eventually converted to the *threo N*-Boc aminoepoxide **14** via the *threo* amio-diol **69** using a Mitsunobu reaction (Scheme 23).[70]

Kang *et al.* reported an interesting approach using iodocyclization technology (Scheme 24).[71] Chiral butenediol **90** was treated with trichloroacetonitrile and DBU, and the resulting imidate was cyclized with IBr to give the intermediate **91** in excellent yield. After purifying **91** by column chromatography, compound **91** was hydrolyzed and cyclized with $NaHCO_3$ to give aziridine, which was further protected with Boc_2O. The resultant *N*-Boc aziridine **92** was reacted with Grignard reagent after protection of the diol with TMSCl to afford the desired *threo* amino-diol **69**, which was then successfully converted to the *threo N*-Boc aminoepoxide **14**.

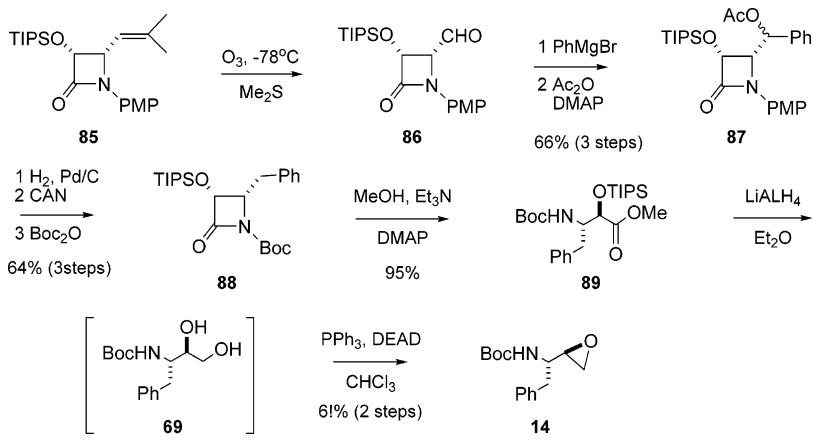
Scheme 24



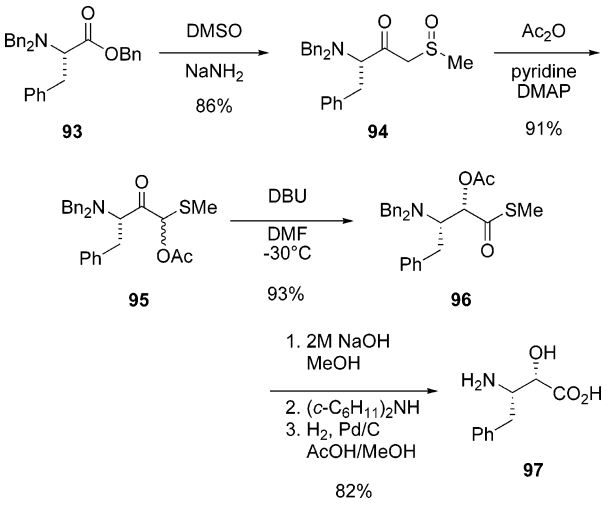
Recently, we reported a new synthetic method for *erythro*-(2*S*,3*S*)-AHPBA (**97**) which involves a Pummerer rearrangement of the β-ketosulfoxide **94** derived from *N*,*N*-dibenzyl phenylalanine benzyl ester **93** followed by highly diastereoselective acyl migration (Scheme 25).[72]

In the course of the above exploration, we realized that the Pummerer rearrangement product **98** could be reduced to give the *threo* amino-diol **99** as a major isomer in a ratio of 89:11. After exchanging the protecting group, *N*-Boc amino-diol **69** was allowed to react with trimethyl orthoacetate followed by acetyl bromide to give bromohydrin acetate **101** in 57% yield. Treatment of **101** with a base successfully afforded the *threo N*-Boc aminoepoxide **14** in 99% yield (Scheme 26).[73]

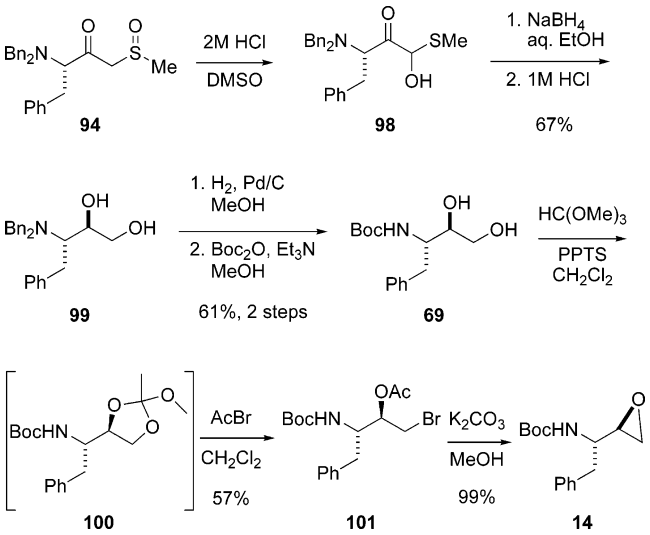
Scheme 23



Scheme 25



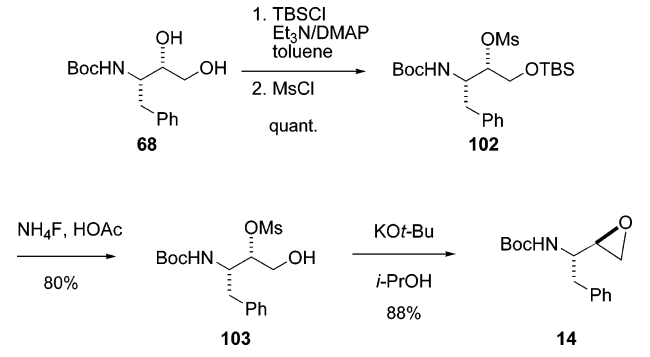
Scheme 26



3.2. Synthesis from *erythro N*-Protected 3-Amino-4-phenylbutan-1,2-diol with Inversion of the Configuration at the 2 Position

Xu *et al.* at Bristol-Myers Squibb reported that the *erythro* amino-diol **68** could be converted to the *threo N*-Boc-amino-epoxide **14** by a four-step sequence of (1) TBS protection of the primary alcohol, (2) mesylation of the secondary alcohol, (3) deprotection of the primary alcohol, and (4) epoxide formation under alkaline conditions (Scheme 27).[74] As described, the diol **68** can be obtained via Sharpless asymmetric epoxidation and ring opening by azide, followed by reduction and Boc protection (Scheme 20).[55]

Scheme 27



3.3. Synthesis from *erythro N*-Protected 3-Amino-1-chloro-4-phenyl-2-butanol with Inversion of the Configuration at the 2 Position

As mentioned above, preparative methods for the *erythro* (2*S*,3*S*)-aminoalcohol **63** have been established for the manufacture of an intermediate for Amprenavir. Several groups have reported the synthesis of the *threo N*-Boc aminoepoxide **14** using **63** as the starting material (Scheme 28).[42,75,76]

The key technology for each method is different—being largely dependent on the means employed to perform the stereoinversion at the 2-position. Scientists at Kaneka obtained the *threo N*-Boc aminoepoxide **14** by treatment of **63** with Bu_4NOAc followed by mesylation and epoxidation with a base (method A).[75] On the other hand, Aerojet first performed the mesylation of **63** to yield the chlorohydrin mesylate **106**, which was then subjected to an S_N2 reaction with cesium acetate in the presence of crown ether to invert the configuration. The resultant chlorohydrin acetate **107** was converted to the *threo N*-Boc aminoepoxide **14** in high yield (method B).[42] Researchers at Phoenix reported the synthesis of **14** by a Mitsunobu reaction of the *erythro* aminoalcohol **63** with *p*-nitrobenzoic acid followed by epoxidation under alkaline conditions (method C).[76]

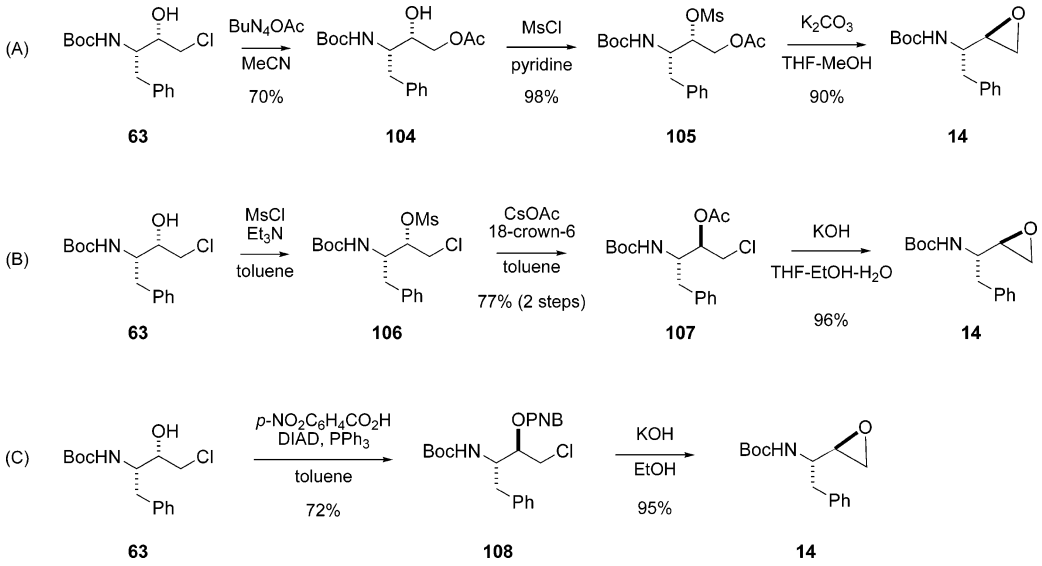
3.4. Synthesis by Epoxidation of *N*-Protected (3*S*)-3-Amino-4-phenyl-1-butene

Luly *et al.* at Abbott reported stereoselective epoxidation of the *N*-protected allylamine **67** with MCPBA (Scheme 29).[77] *N*-Protected (3*S*)-3-amino-4-phenyl-1-butene (**67**) was prepared in four steps from L-phenylalanine (**22**) by reduction, Boc protection, and pyridine/SO_3 oxidation followed by a Wittig reaction. The epoxidation of **67** proceeded with high *threo* selectivity in modest yield. Although the reaction sequence appears very simple and attractive for industrial synthesis, it has its drawbacks in terms of the epimerization of the aldehyde intermediate **13** during the Wittig reaction and the difficulties associated with isolating and purifying the *threo N*-Boc aminoepoxide **14**. It is noteworthy that an excess of MCPBA gave better *threo* selectivity, since the *erythro* isomer **10** decomposed faster than the desired product **14** in the presence of MCPBA.[78]

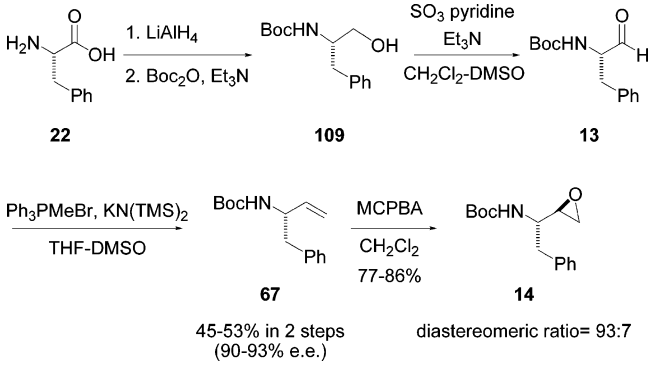
3.5. Synthesis via the *threo* Selective Reduction of *N*-Protected (3*S*)-3-Amino-1-halo-4-phenyl-2-butanone

N-Alkoxycarbonyl α-aminoalkyl α′-halomethyl ketones used for the synthesis of *erythro N*-protected aminoepoxides are also good intermediates for the synthesis of *threo N*-protected aminoepoxides: as mentioned previously, reduction with $NaBH_4$ preferentially affords *erythro* aminoalcohols. On the other hand, the *threo* selective reduction of the halomethyl ketones can be achieved with $LiAl(Ot\text{-}Bu)_3H$ in Et_2O to give the desired *threo* aminoalcohols in a diastereomeric ratio of 83:17 in high yield (Scheme 30). Although the reaction for the bromomethyl ketone **110** was reported more than 10 years ago,[19] it has since been confirmed that the reduction of the chloromethyl ketone **40** also proceeds with a similar selectivity.[42,79] A possible concern for this reduction might be that solvents other than Et_2O may not allow good selectivity.

Scheme 28

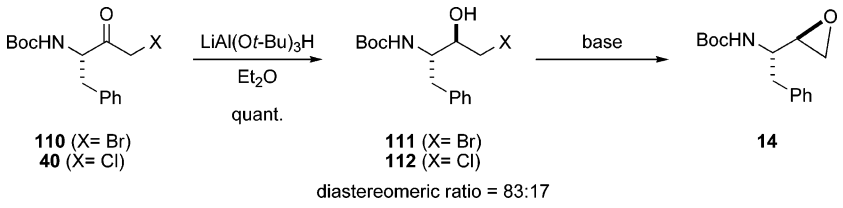


Scheme 29

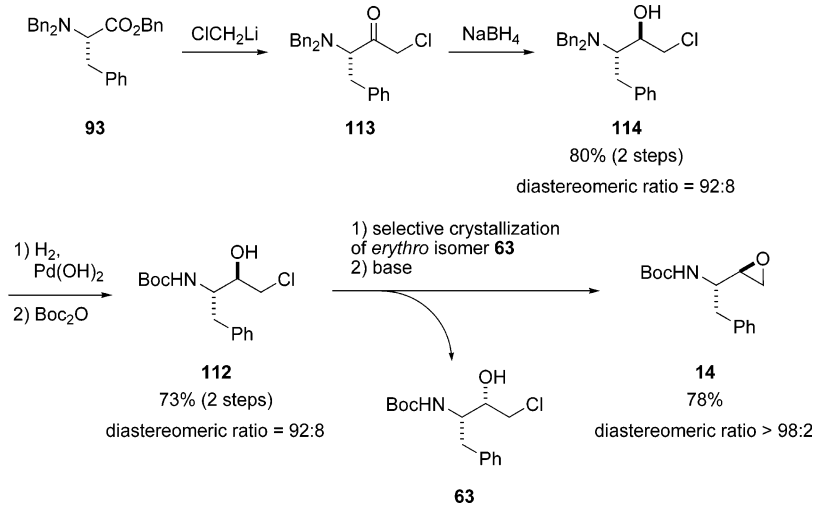


There have been several reports describing the attainment of still higher selectivities by means of asymmetric transfer hydrogenation with a rhodium catalyst[49] and enzymatic reduction.[80,81] The *threo* aminoalcohol **112** thus obtained has higher solubility by far in a variety of solvents than the corresponding *erythro* isomer **63**, and it is consequently very hard to eliminate the impurity **63** by simple crystallization. The differing solubilities of these diastereomers **112** and **63** may derive from different modes of intermolecular hydrogen-bonding networks in these two crystals.[82] To overcome such difficulties in the purification of the *threo* aminoalcohol **112**, a separation method using countercurrent chromatography with simulated moving bed (SMB) on an industrial scale was

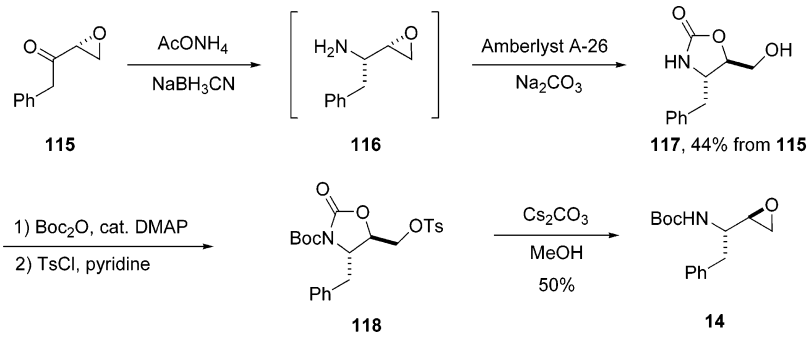
Scheme 30



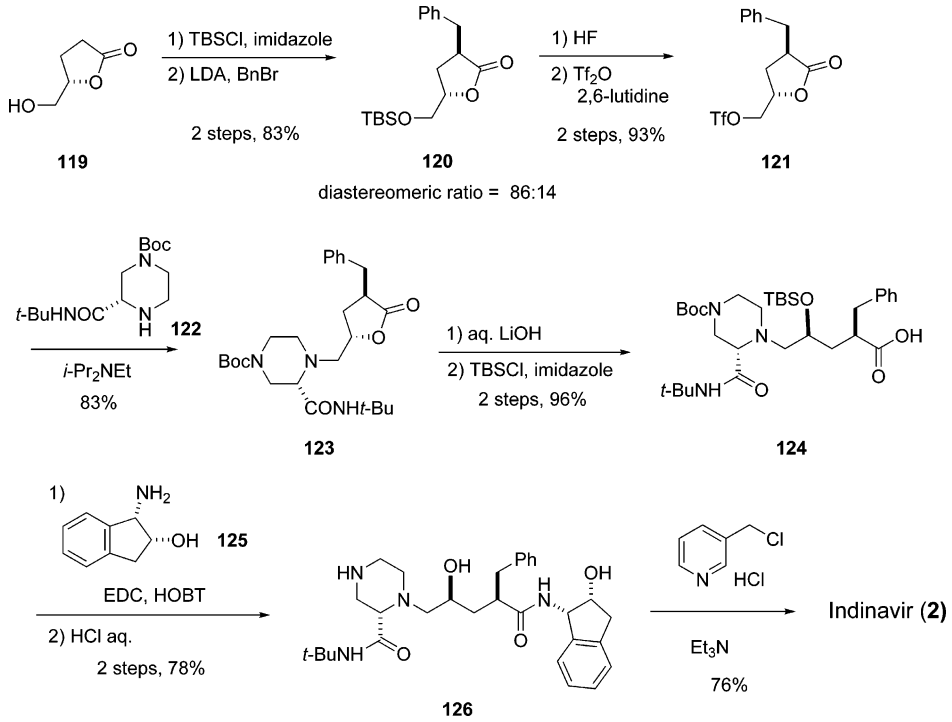
Scheme 31



Scheme 32



Scheme 33



reported.[83] Another interesting approach is to remove impurity **63** by crystallization to give a solution of the *threo* aminoalcohol **112** in a diastereomeric ratio of better than 98:2.[79]

Barluenga *et al.* reported a highly *threo* stereoselective reduction of *N*,*N*-dibenzyl chloromethyl ketone **113** with $NaBH_4$ to give the corresponding *threo* aminoalcohol **114** in a diastereomeric ratio of 92:8.[16] Applying this technology, we developed a process for the synthesis of *threo N*-Boc aminoepoxide **14** (Scheme 31).[84] Although it was difficult to eliminate the *erythro* isomer without chromatography at the compound **114** stage, after conversion to the *threo N*-Boc aminoalcohol **112** by exchanging the protecting group from dibenzyl to Boc, the resulting *erythro* isomer **63** could be successfully eliminated by crystallization as described above.[79] Finally, the desired product **14** could be obtained by treatment with a base.

The process validity of the above has been confirmed on an industrial scale. It is noteworthy that, starting with L-phenylalanine, the desired *threo N*-Boc aminoepoxide **14** is obtained in only six steps in high overall yield.

3.6. Other Miscellaneous Methods

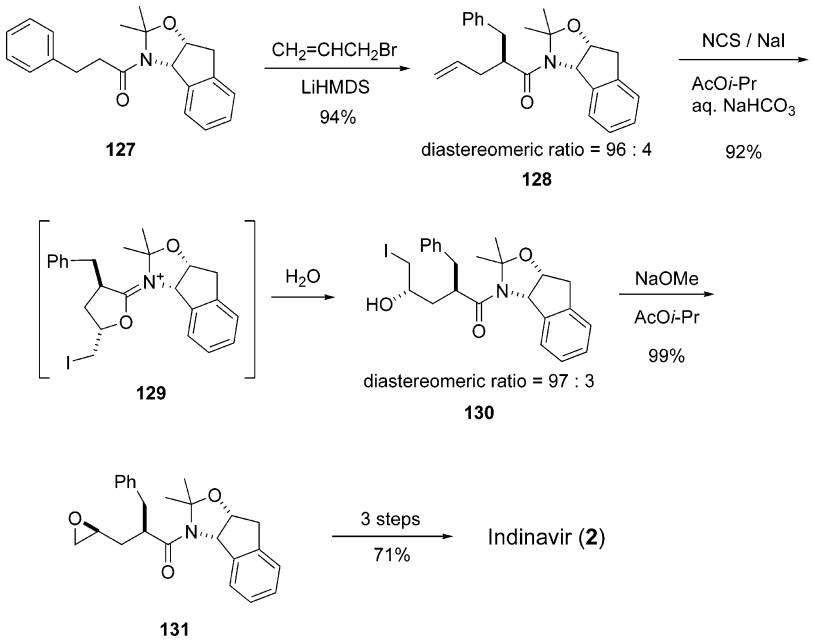
Pegorier *et al.* reported that the unprotected aminoepoxide **116**, which was prepared *in situ* by reductive amination of the chiral epoxy-ketone **115**, gave *trans* oxazolidinone **117** by the treatment with Amberlyst in 44% yield from **115**.[85] Under these conditions, the intramolecular ring opening of the epoxide takes place with the inversion of the configuration at the chiral center. The resulting oxazolidinone **117** was successfully transformed into the *threo N*-Boc aminoepoxide **14** by Boc protection and tosylation followed by the treatment with base (Cs_2CO_3) in MeOH (Scheme 32).[85]

4. Synthesis of the Core Molecule of Indinavir

Indinavir (**2**) was developed by Merck as a potent HIV protease inhibitor and approved by the FDA in 1996.[86,87] The original synthetic process for Indinavir used dihydro-5-(*S*)-(hydroxymethyl)-3(*2H*)-furanone (**119**) as a starting material. The furanone was transformed into the key core intermediate **121** via a four-step process involving diastereoselective benzylation. The core **121** was allowed to react with the left wing—the piperazine carboxamide[122,88]—and then was coupled with the right wing—the optically active aminoindanol **125**[89] (Scheme 33).[87]

This medicinal chemistry process made it possible to produce Indinavir on a 10 g scale affording the product in 35% overall yield from the chiral furanone **119**. From an industrial point of view, however, it was not a satisfactory process because it required chromatographic purification and

Scheme 34

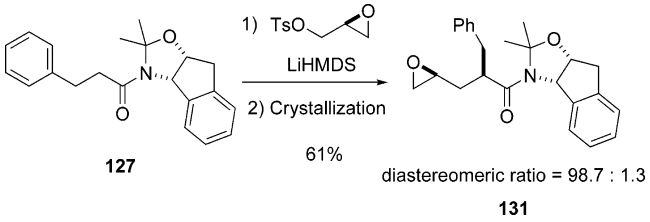


the use of expensive reagents such as triflic anhydride and TBSCl. In the meantime, Maligres *et al.* in the process research group at Merck developed an excellent industrial process involving the chiral epoxide **131** as the key core intermediate (Scheme 34).[90,91]

The phenylpropionyl amide **127**, readily prepared from the chiral aminoindanol **125**[89] in two steps, was allowed to react with allyl bromide to give the allylated product **128** in a high diastereomeric ratio of 96:4 and high yield: 94%. After several unsuccessful attempts at the *syn*-epoxidation of **128**, it was eventually found that the reaction of **128** with N-chlorosuccinimide (NCS) in the presence of NaI under two-phase reaction conditions proceeded well to afford the iodohydrin **130** in 92% yield with high diastereoselectivity (97:3). The reaction mechanism, involving intramolecular iodoimidation to the olefinic bond, has been referred to above. The last step for the core synthesis was the base treatment of the iodohydrin **130** to produce the chiral epoxide **131**. The characteristic feature of this novel process was the construction of the new optically active center of the core by taking advantage of the chirality of the side chain molecule. An alternative process using (*S*)-glysidyl tosylate instead of allyl bromide was also developed (Scheme 35).[92]

This procedure appears very attractive because of the reduced number of reaction steps, although the former method might be more practical on an industrial scale from the point of view of cost.

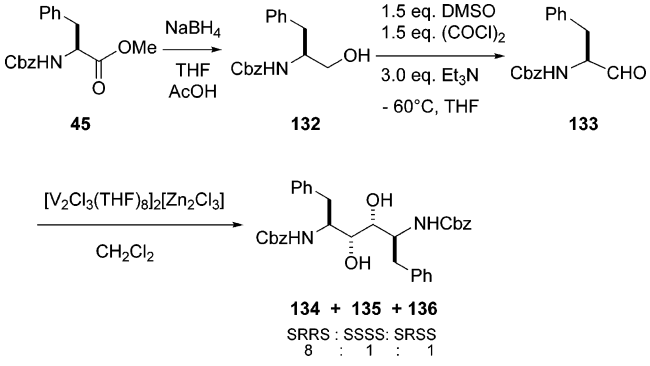
Scheme 35



5. Synthesis of the Core Molecule of Ritonavir and Lopinavir

Ritonavir (**3**) was approved by the FDA in 1996 as the second protease inhibitor.[93,94] Lopinavir (**6**), having the same central core as **3**, was also approved in 2000 as a second-generation HIV protease inhibitor.[95,96] Recently, **3** has attracted much attention for its use in combination therapy, since the coadministration of small doses of **3** with several agents brings about substantial improvements in terms of bioavailability and activity against HIV.[97−99] In the early phases of the development, the core molecule was prepared according to the process shown in Scheme 36.[100,101] *N*-Cbz-phenylalaninol **132** prepared from L-phenylalanine was subjected to Swern oxidation to give *N*-Cbz-phenylalaninal **133**. The homocoupling of the resulting aldehyde **133** was carried out with $[V_2Cl_3(THF)_6]_2[Zn_2Cl_4]$ according to Pedersen's procedure to give a 8:1:1 mixture of the *SRRS* isomer **134**, the *SSSS* isomer **135**, and the *SRSS* isomer **136**, respectively.

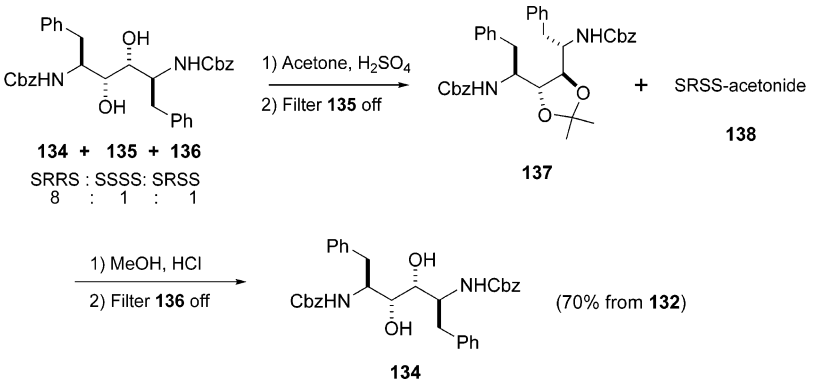
Scheme 36



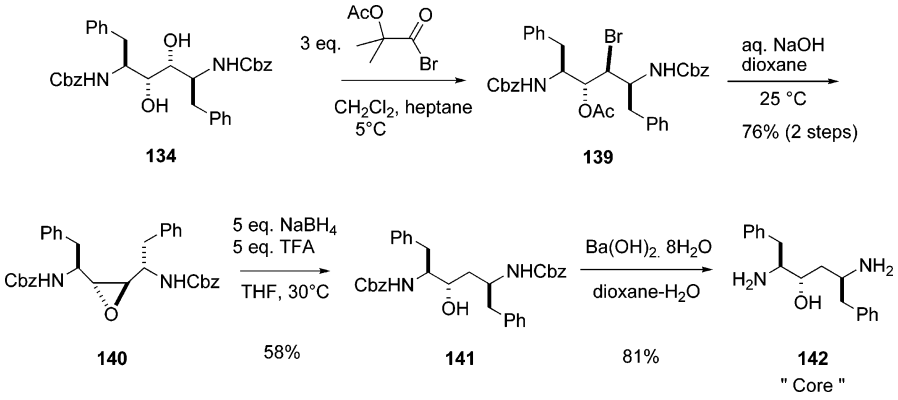
The mixture was then subjected to acetonide formation to eliminate the insoluble *SSSS* isomer **135**, followed by acidic hydrolysis to afford the pure *SRRS* isomer **134** after removing a small amount of the *SRSS* isomer **136** by crystallization (Scheme 37).

The isomerically pure diol **134** was treated with α-acetoxyisobutyryl bromide to give the bromohydrin acetate **139**, which was then converted to the epoxide **140** under alkaline conditions. The reduction of the epoxide **140** in the presence of CF_3CO_2H provided the monool **141**. Deprotection of the

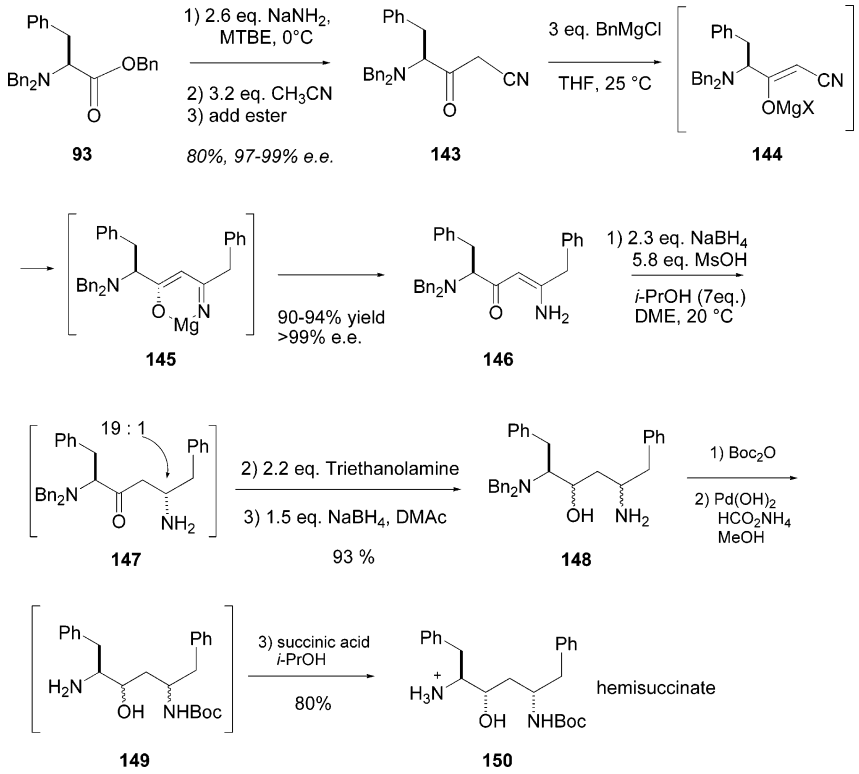
Scheme 37



Scheme 38



Scheme 39



Cbz group with $Ba(OH)_2$ gave the desired core molecule **142** (Scheme 38).

Since the diaminoalcohol **142** thus obtained has two amino groups, differentiation between them proved difficult. However, the scientists at Abbott overcame this problem by the discovery that the benzeneboronic acid reacts with the diamono alcohol **142** to give the six-membered ring selectively, so that the regioselective modification of the diaminoalcohol **142** became possible. This process took advantage of the physical and chemical properties of each intermediate to obtain the pure product, although industrialization was unfortunately deemed to be too difficult because it not only

required too many reaction steps but also employed toxic low valent vanadium in large quantities. Some years later, however, Abbott scientists developed a new breakthrough process for the core molecule (Scheme 39).[102−105]

The *N*,*N*-dibenzyl-phenylalanine benzyl ester **93** was subjected to cyanomethylation with CH_3CN and $NaNH_2$ to obtain the ketone **143**, which was subsequently allowed to react with BnMgCl followed by hydrolysis to afford the enaminoketone **146** in good yield. The enaninoketone **146** was first treated with $NaBH_4$ in the presence of MsOH to give the aminoketone intermediate **147**, which was further reacted with an extra amount of $NaBH_4$ to afford the *N*,*N*-dibenzyl-protected diaminoalcohol **148**. Compound **148** was then protected with Boc_2O and the dibenzyl group was removed by catalytic hydrogenolysis to give the desired core **149**. Although the diaminoalcohol contained several isomers as impurities in this stage, the pure diaminoalcohol was obtained by crystallization as the succinate form **150**.[103] This core succinate **150** is very useful because one wing is already protected by a Boc group. This process therefore constituted a substantial improvement on the first synthesis described above.

6. Conclusion

Recently, gene engineering technologies including viral genomics have made an enormous contribution to elucidating the roles of proteins (enzymes) in disease conditions. As a result, molecules for inhibiting specific enzymes have been rationally designed on the basis of three-dimensional analyses. These molecules often feature peptide mimetics comprising chiral aminoalcohol functional groups because of their structural diversity and versatility; the success of the HIV protease inhibitors is a good example of this.

As described above, asymmetric synthetic processes for both *erythro* and *threo* 3-amino-1,2-epoxides have been well established, thus facilitating the industrial scale production of several HIV protease inhibitors. The achievements in the synthesis of chloromethyl ketones are quite noteworthy in this regard. The methodologies developed as a result of these studies will also possibly further contribute to the development of novel drug substances for other conditions, such as secretase inhibitors for Alzheimer's disease and caspase inhibitors for inflammatory conditions—compounds that utilize not only natural amino acids but also a variety of unnatural amino acids which are currently commercially available in large quantities.

7. Note Added after ASAP Publication

This review was posted ASAP on March 25, 2006. The last sentence in section 3.2 has been revised. This review was reposted on March 29, 2006.

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