Overview of the Synthesis of Optically Active 3-Amino-2-Hydroxy-4-Phenylbutyric Acids, Key Intermediates for Numerous Bioactive Compounds

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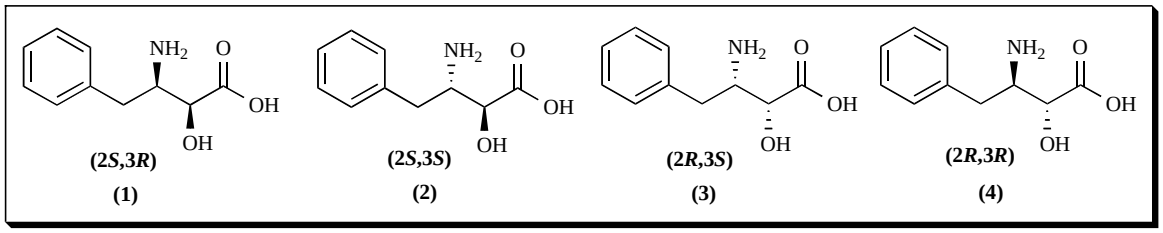
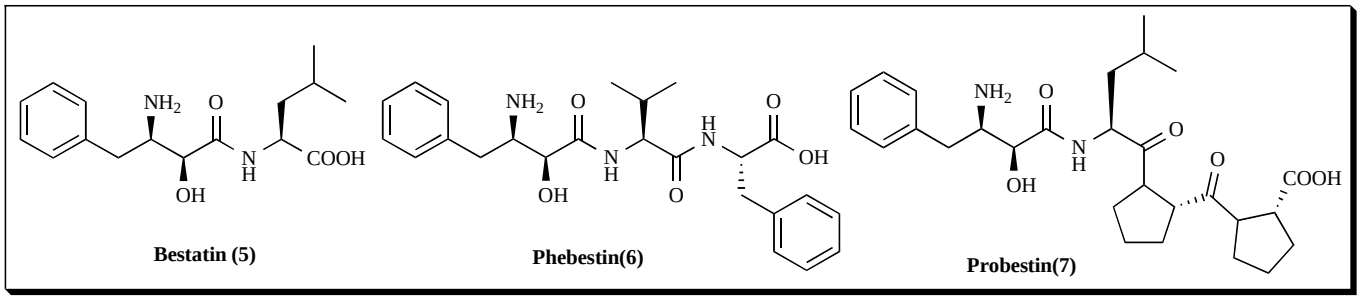
Abstract: 3-Amino-2-hydroxy-4-phenylbutyric acids (AHPA or alternatively abbreviated AHPBA) serve as chiral building blocks for various bioactive compounds including aminopeptidase N (APN) inhibitors, HIV-l protease inhibitors, and renin inhibitors. The synthesis of α-hydroxy-β-amino acids has therefore attracted considerable interest in recent years and various synthetic approaches have been developed to complete their synthesis. These strategies include utilization of enantiopure starting materials like sugars and amino acids and introduction of bulky groups to achieve the desired stereoselectivity and asymmetric catalysis using enzymes or inorganic catalysts to achieve the desired stereochemistry. This review will discuss these synthetic strategies.

Keywords: AHPA, asymmetric synthesis, catalysts, chiral synthons, enantioselective synthesis, stereoselective synthesis.

INTRODUCTION

3-Amino-2-hydroxy-4-phenylbutanoic acid is a vital peptidomimetic amino acid with a wide range of biological activities. This compound containing two chiral centers constructs four isomers **(1-4)** with structures that are present in many medicinally important molecules. Several recently isolated aminopeptidase inhibitors, *viz*. Bestatin **(5)**, Phebestin **(6)**, and Probestin **(7)**, contain a (2*S*,3*R*)-configuration fragment in their structures [1]. Among them, Bestatin is the only marketed APN inhibitor for leukaemia therapy at present, and obtaining optically active (2*S*,3*R*)-AHPA represents a considerable challenge in the complete synthesis of Bestatin. In addition, (2*S*,3*S*)-AHPA is used as a crucial building block for some HIV-l protease inhibitors presented in KNI 272 **(8)** [2] and as an essential component of the antimalarial KNI 227 **(9)** [3]. The (2*S*,3*R*)-AHPA [5,6]. To the extent known, however, no review has sought to summarize the stereoselective synthesis of all four AHPA isomers, so the current article will mainly discuss strategies to achieve a higher chemical yield and also better stereoselectivity.





(2*R*,3*S*)-configuration also provides a core unit for several renin inhibitors **(10)** [4]. Therefore, the stereoselective synthesis of AHPAs has attracted considerable attention in recent years. Recently, several reviews have focused particularly on the synthesis of

THE SYNTHESIS OF AHPAs

In order to obtain optically pure AHPAs, different strategies have been introduced and adopted to achieve the goal. These methods include asymmetric catalytic synthesis, enzymatic kinetic resolution, and the use of chiral auxiliaries and chiral building blocks. In order to effectively, succinctly, and logically summarize these methods, they have been classified here according to the starting materials and special reagents involved.

1. STARTING FROM CHIRAL SUBSTRATES

1.1. From Phenylalanine and its Derivatives

A: The method used to synthesize a mixture of (2*S*,3*R*) and (2*R*,3*R*)-AHPAs is shown in Scheme **1.1** [7]. N-benzyloxycarbonyl-D-phenylalanine was coupled with pyrazole to provide a crystalline product in a 95% yield, and this was then reduced with lithium aluminum hydride. The corresponding aldehyde was treated with sodium hydrogen sulfite to yield a solid adduct that was transformed into cyanohydrin by treatment with sodium cyanide. The

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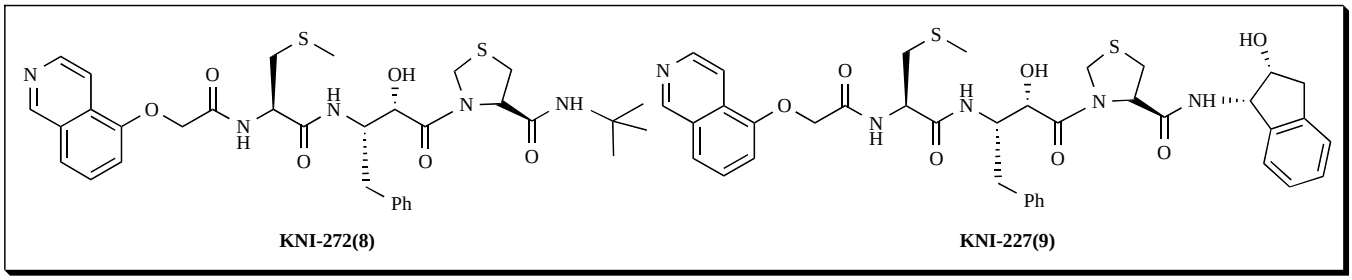
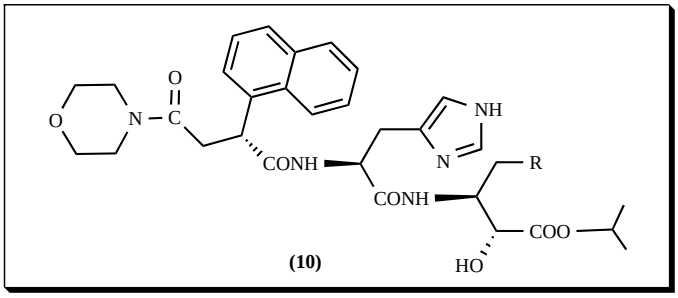


KNI-272(8) **KNI-227(9)**

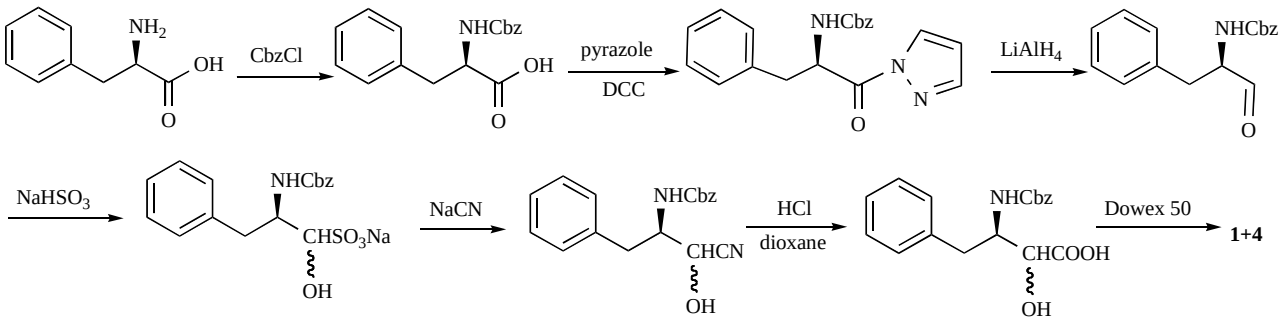


(10)

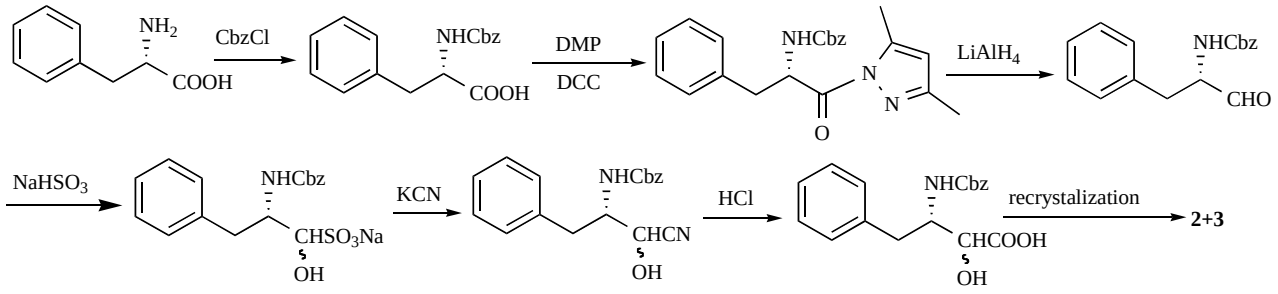
cyanohydrin was hydrolyzed with hydrochloric acid to provide a mixture of (2*R*,3*R*)- and (2*S*,3*R*)-AHPAs. The latter was separated from its diastereoisomer by Dowex 50 chromatography using linear gradient elution comprised by pyridine-acetate buffer. Later, Umezawa *et al*. improved this method to successfully convert the configuration from **4** into **1** through the key formation of oxazoline [8].

The same protocol was used to prepare a mixture of (2*R*,3*S*)- and (2*S*,3*S*)-AHPAs from L-phenylalanine (Scheme **1.2**) [9]. Resolution of the diastereoisomeric mixture of AHPAs was achieved by fractional crystallization of the N-benzyloxycarbonyl derivatives. (2*S*,3*S*)-AHPA was crystallized from ethyl acetate-petroleum ether and (2*R*,3*S*)-isomer was precipitated with brucine from mother liquors. Another practical reagent, diisobutylaluminum hydride (DIBAH), was used to reduce the carbonyl group and is shown in Scheme **1.3** [10]. Resolution of the diastereomers was accomplished by preparative TLC using ethyl ester as a developing agent.

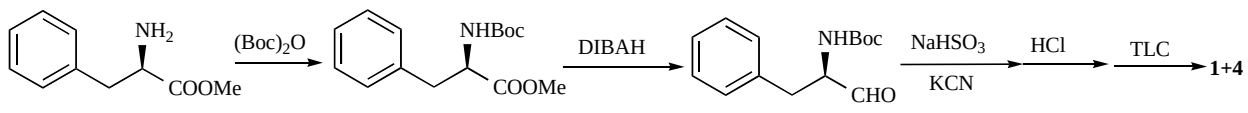
Several modifications have been made to the standard $LAlH_4$ reduction methodology for reduction of the Weinreb amide to aldehyde (Scheme **1.4**) [11,12]. N-O-dimethyl hydroxylamine hydrochloride was introduced to activate the carboxyl group in place of 3,5-dimethylpyrazole. The desired aldehyde was obtained with



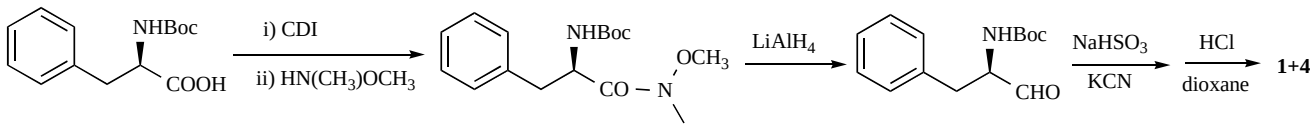
Scheme 1.1.



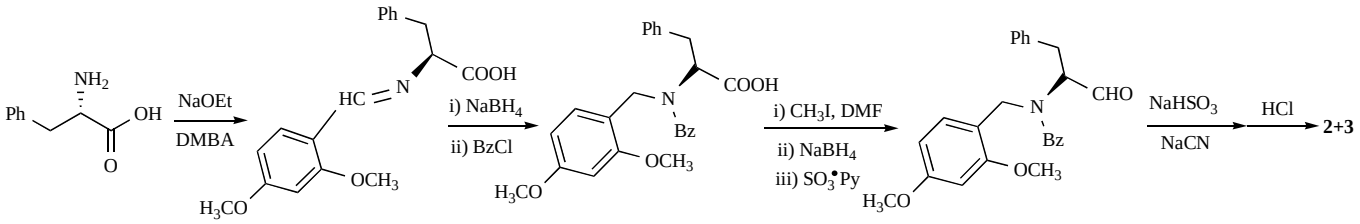
Scheme 1.2.



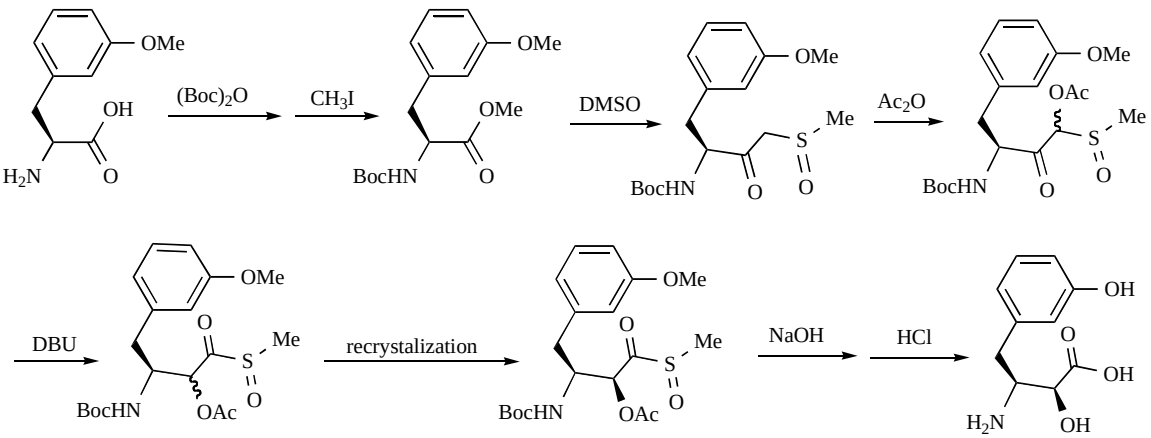
Scheme 1.3.



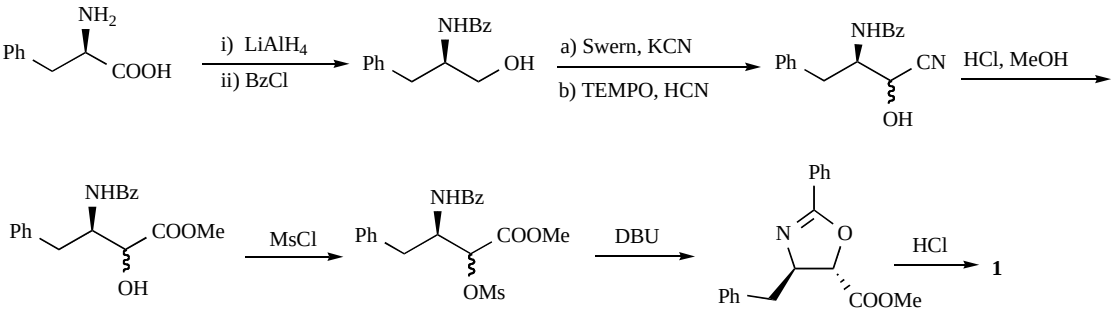
Scheme 1.4.



Scheme 1.5.



Scheme 2.



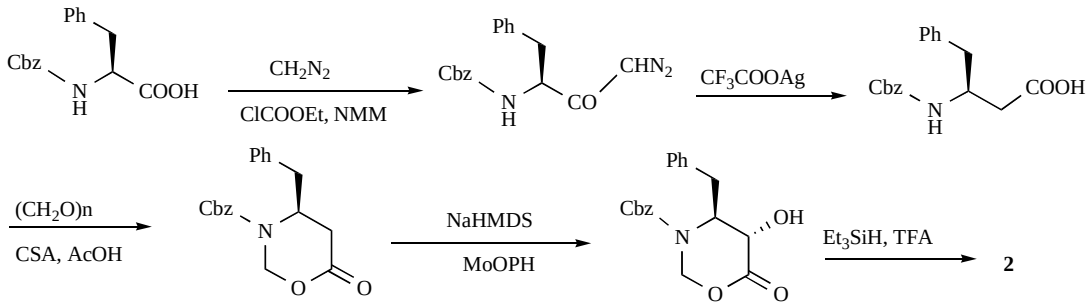
Scheme 3.

minimal C-3 epimerization (< 1%) since the Boc-amino aldehyde was prone to racemization.

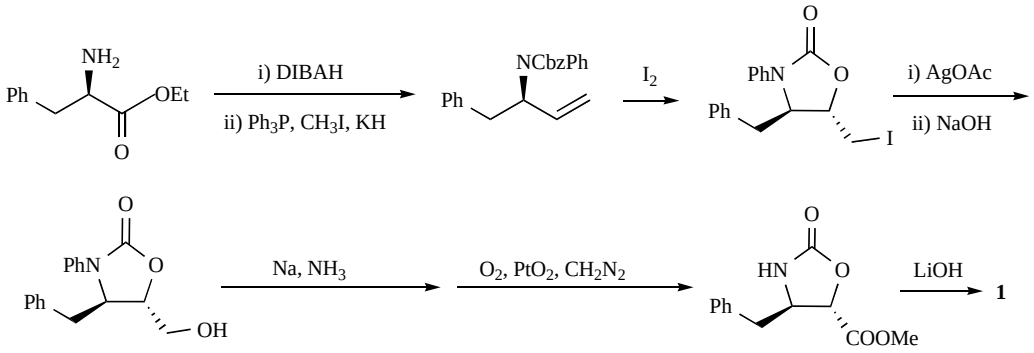
In addition to carboxyl group activation, the bulkiness of the N-protecting group is also considered to govern stereoselectivity. One creative tactic as shown in Scheme **1.5** was used by Ru Qi *et al.* to improve regioselectivity [2]. Based on the assumption that poor cyano group stereoselectivity was partially due to the slight spatial effect of the N-protecting group, a bulkier group was introduced, *viz.* 2,4-dimethoxybenzaldehyde as the protecting group to enhance selectivity. The 2*S* to 2*R* configuration ratio was increased from 42:58 to 67:33. Resolution of the diastereoisomeric mixture of AHPAs was achieved by recrystallization from ether.

B: Mimoto *et al.* [13] found that classic methods involving cyanohydrin could not provide the desired product in a satisfactory yield with AHPA derivatives having 3-methoxyl due to their instability under acid hydrolysis conditions. Thus, another method was introduced for *α*-hydroxy-β-amino carboxylic acids (Scheme **2**). The reaction of N-Boc-protected-L-3-methoxyphenylalanine methyl ester with the carbanions derived from dimethyl sulfoxide (DMSO) yielded a diastereomixture of β-ketosulfoxide, and α-ketohemimercaptal acetate was obtained *via* 1,4-acyl transfer in enolate form in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The diastereomeric ratio (2*S*/2*R*) was about 3:2, and the desired (2*S*,3*S*)-enantiomer was easily separated by recrystallization from hexane/ethyl acetate. Exceptional stereoselectivity was attributed to acetyl migration with kinetically controlled protonation of DBU complex from the less hindered *α*-face, leading to the (2*S*)-stereochemistry that observed [14].

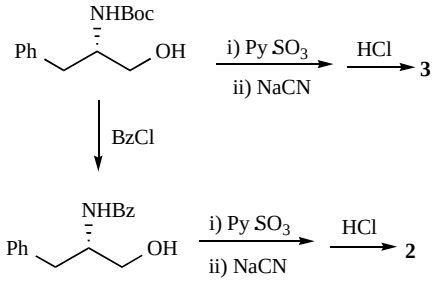
C: α-Amido aldehydes are known to be able to isomerize after the oxidation/addition sequence. Tasic *et al.* described a new strategy to obtain the desired stereochemistry depending on the conversion of stereoisomeric cyanohydrins into *trans*-oxazolines [15]. This synthesis, shown in Scheme **3**, started with the formation of α-amido alcohol according to the literature [16]. The oxidation/cyanide addition sequence yielded cyanohydrin, which underwent hydrolysis, esterification, mesylation, and cyclization by the



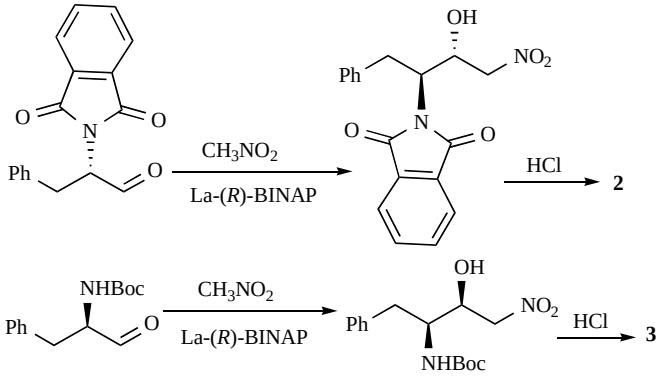
Scheme 4.



Scheme 5.



Scheme 6.1.



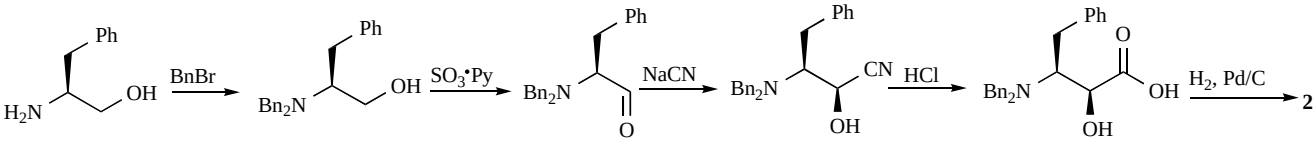
Scheme 6.2.

addition of DBU to provide *trans*-oxazoline in a 70 % yield. Its subsequent hydrolysis resulted in (2*S*,3*R*)-AHPA in an 88% yield. Cyanohydrin prepared from protected α-amino aldehyde was deemed to be the key intermediate to determine the steric configuration, so several reagents have been used. The combination of 2,2,6,6-tetramethylpiperidine- 1-oxyl (TEMPO) oxidation and hydrogen cyanide provided an almost quantitative yield (98%) with 93% *ee* compared to only a 66% yield utilizing Swern oxidation and potassium cyanide. Andres *et al.* [17] reported that the diastereoselective cyanation of chiral α-amino aldehydes with diethylaluminum cyanide yielded *anti:syn*-product (75:25) and that the mixture was easily separated by flash chromatography.

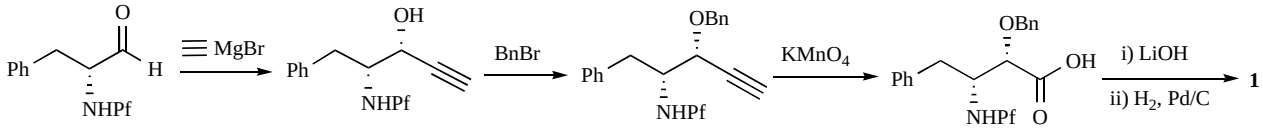
D: To obtain (2*S*,3*S*)-AHPA, Hughes *et al.* introduced a worthwhile route *via* 1,3-oxazinan-6-one starting from N-protected phenylalanine (Scheme **4**) [18,19]. The amino acid derivative was allowed to react with CH_2N_2 to yield the corresponding diazoketone coupling with ethyl chloroformate and N-methyl morpholine (NMM) *in situ*. Subsequent Wolff rearrangement yielded a product that was further formulated into the key intermediate oxazinanone. Then, 5-hydroxylation of oxazinanone using molybdenum oxide pyridinium hexamethyl phosphoramide complex (MoOPH) provided the desired configuration, and the final reductive cleavage of oxazinanone yielded the required product. Exceptional *trans*-selectivity is contributed to face discrimination, corresponding to an electrophilic attack prompted both by the effect of MoOPH and chiral properties of the reactant itself.

E: Kobayashi *et al.* [20] used D-phenylalanine ethyl ester to produce chiral allylamine by reduction and a subsequent Wittig reaction (Scheme **5**). Treatment of protected amine with iodine predominantly yielded *trans*-iodocarbamate (*trans:cis* = 6.7:1), followed by the formation of alcohol, the benzyl group of which was then removed by Birch reduction. Jones oxidation yielded methyl ester, and the ring of which was opened through alkaline hydrolysis, resulting in optically active AHPA. The total yield of this route from D-phenylalanine ethyl ester was about 17% and the key step was the formation of *trans*-iodocarbamate by 1,2-asymmetric induction of iodocyclocarbamation in acyclic allylamine.

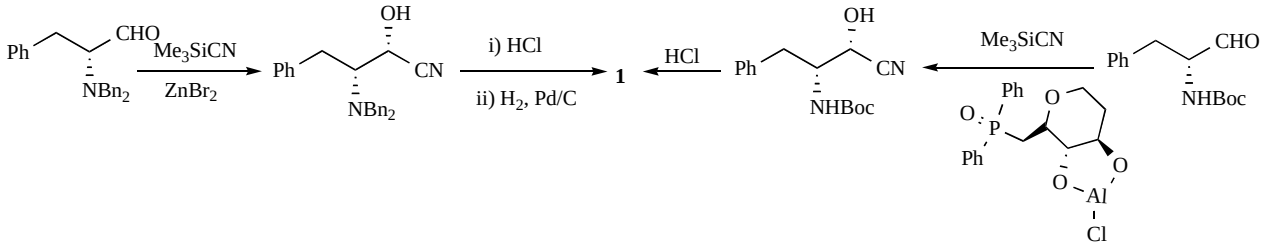
F: During an investigation of the renin inhibitory activity of Boc-L-cyclohexylalaninal, an effective method of the stereoselective synthesis of optical α-hydroxy-β-amino acids was discovered [4]. The (2*R*,3*S*)-configuration was efficiently prepared from Boc-L-phenylalaninol and the (2*S*,3*S*)-configuration from Bz-L-phenylalaninol. Specific reaction conditions are shown in Scheme



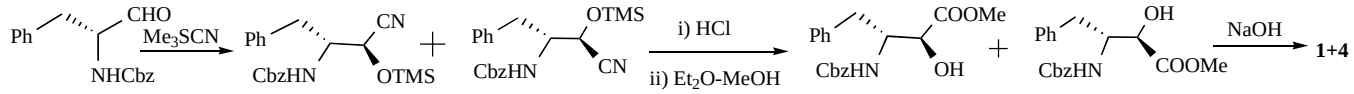
Scheme 7.



Scheme 8.



Scheme 9.1.



Scheme 9.2.

6.1. Harada *et al.* [21] successfully achieved conversion from the 2*R* to the 2*S* configuration *via* the formation of oxazoline. Likewise, Mitsuda [22] also reported the importance of the spatial effect of the N-protecting group. Different N-protecting groups can lead to different stereoselectivity through stereoselective addition of nitromethane, as in Scheme **6.2**. For example, a *trans*-product was predominantly obtained when a phthaloyl group was selected as the protecting group, while a Boc-group induced *threo*-selective addition.

G: Another method [23] (Scheme **7**) starting from (*S*)-2-amino-3-phenylpropanol used the following successive reactions: N-protection, Parikh-Doering oxidation, hydrocyanation, hydrolyzation and benzyl deprotection. This method successfully yielded (2*S*,3*S*)-AHPA in priority with 2*S*:2*R* = 5:1, which could then be readily isolated by column chromatography. The obvious advance is that the entire process is relatively short. However, diastereoselectivity did not improve to the same extent since it relies on the minor benzyl groups to control stereochemistry.

H: Another route for (2*S*,3*R*)-AHPA was completed beginning with a Grignard reaction by protected D-phenylalaninal resulting in a predominant *syn*-product (*syn*:*anti* = 9.5:1) (Scheme **8**) [24]. These isomers were then separated by flash chromatography to yield a single diastereomer. O-benzylation and subsequent oxidation by $KMnO_4$ furnished **1** after a two-step deprotection. CH-π interaction and chelation control in an aromatic aminoaldehyde were utilized to achieve highly diastereoselective addition to yield optically active *syn*-aminoalcohol. The overall yield of **1** from α-aminoaldehyde was over 65%.

I: In Scheme **9.1**, synthesis also started with the reaction of N-protected D-phenylpropionaldehyde [25] to yield homologous cyanohydrin. Acidic hydrolysis of cyanohydrin yielded N-protected (2*S*,3*R*)-AHPA, with hydrogenation terminating the entire process. In this method, Me_3SiCN coupling with $ZnBr_2$ was used to control regioselectivity. Another method of catalytic stereoselective cyanosilylation of aldehyde promoted by a bifunctional catalyst was developed by Nogami *et al.* [26]. This was achieved by the enantioselective addition of Me_3SiCN with exceptional stereoselectivity (92% *ee*), which increased the total yield of **1** from phenylalaninal to 75%.

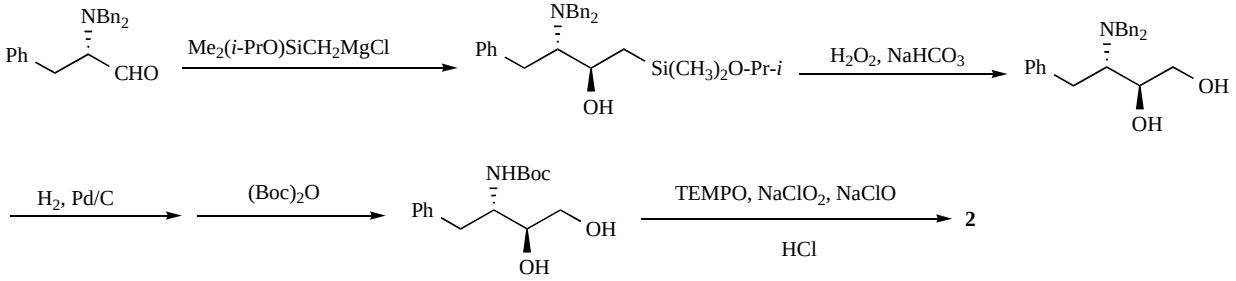
Via the same method, N-Cbz-protected aldehyde was also used as the starting material to achieve the stereoselective synthesis of AHPAs [27], as outlined in Scheme **9.2**. This improved route, which does not require extra deprotection-protection steps compared to those for corresponding N-Boc-protected compounds, leads predominantly to (2*S*,3*R*)-AHPA in a 60% yield.

J: Ikunaka *et al.* [28] managed to obtain (2*S*,3*S*)-AHPBA from (*S*)-2-N,N-dibenzylamino-3-phenylpropanal in an overall yield of about 41% (Scheme **10**). They did so in five steps in which [Me_2(*i*-PrO)$SiCH_2MgCl$] was used for one-carbon homologation to successfully establish the desired configuration. The [$Si(CH_3)_2OPr$-*i*] group appeared to have a spatial effect, augmenting the intrinsic propensities that allowed aldehyde to undergo nonchelation-controlled addition. Zhao's oxidation protocol [29] (TEMPO, $NaClO_2$, NaClO) was used to convert a 1,2-glycol moiety into an α-hydroxy acid motif through regioselective oxidation.

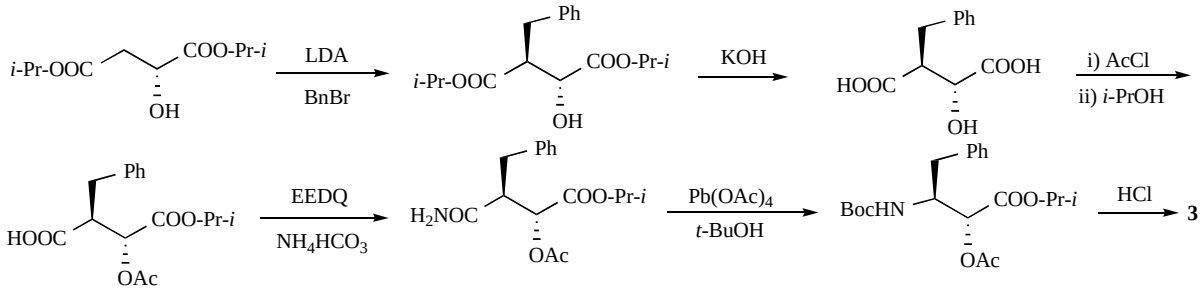
1.2. From Malic Acid Derivatives

A: Based on the available knowledge on the preparation for *erythro*-2-hydroxysuccinic acid derivatives from malic esters [30], Dugger *et al.* [31] devised a new protocol to synthesize (2*R*,3*S*)-AHPA (Scheme **11**), which was prepared beginning with benzylation of a D-malate carboanion. Then the differentiation of the two carboxylates was accomplished through the monoesterization of the carboxyl group vicinal the hydroxyl group *via* a pentacyclic anhydride and the subsequent reaction of IV-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) with NH_4HCO_3 *in situ* yielded amide. Simple hydrolysis after Hofmann degradation furnished the expected compound.

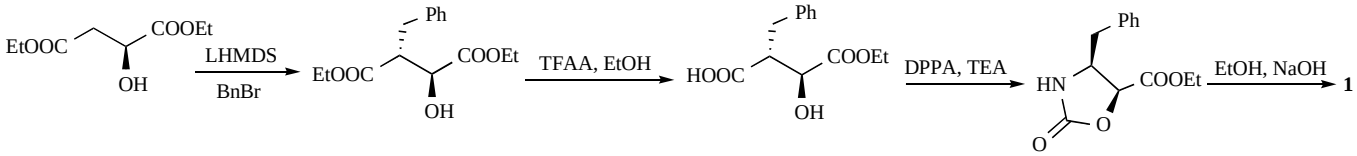
B: Another highly diastereospecific route to (2*S*,3*R*)-AHPA from L-malic acid has also been developed (Scheme **12)** [32]. This



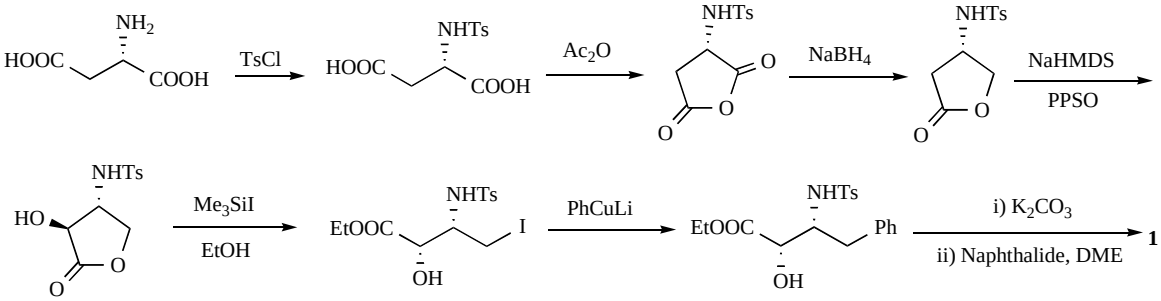
Scheme 10.



Scheme 11.



Scheme 12.



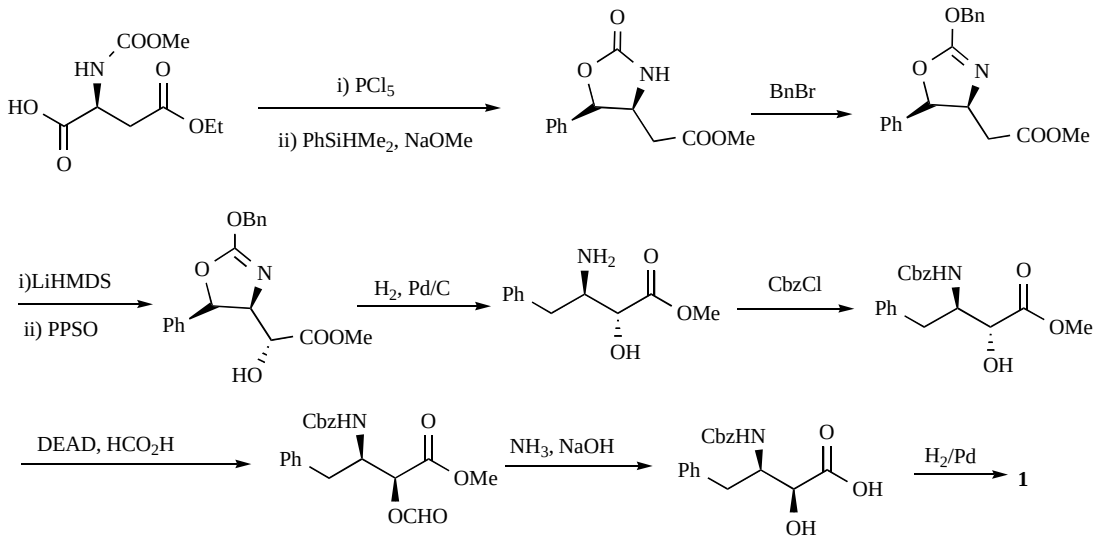
Scheme 13.

approach featured stereocontrolled alkylation of (*S*)-diethy1 malate and proceeded through an oxazolidone *via* Curtius rearrangement. In the process, (*S*)-diethy1 malate was alkylated at a 3*R*:3*S* > 35:1 ratio by displacing lithium diisopropylamide (LDA) [31] with lithium hexamethyldisilazide (LHMDS). The key intermediate oxazolidone was obtained with little loss of diastereomeric purity and was refined by flash chromatography. Final saponification yielded (2*S*,3*R*)-AHPA. Since the optical isomers of malic acid are commercially available, this approach means that all four diastereomers of AHPBA can be obtained *via* the selection of a proper malic acid enantiomer and an additional Mitsunobu inversion of the hydroxy group following alkylation.

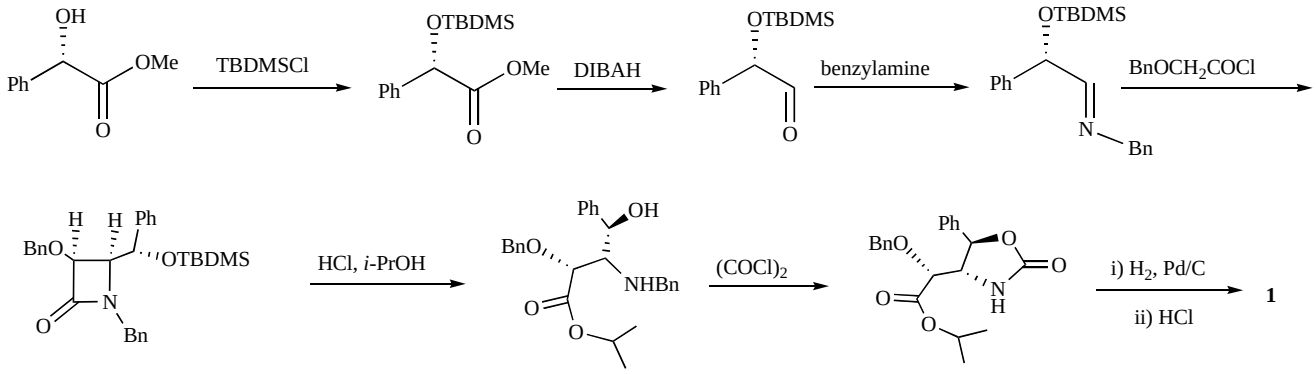
1.3. From Aspartic Acid Derivatives

A: Due to their specific structures, L- and D-aspartic acids can easily be converted into the enantiomeric 3-(tosylamino)butano-4-lactones that serve as versatile templates for preparing β-amino-α-hydroxy acid derivatives in an optically pure form. Jefford *et al.* [33] reported that L-aspartic acid undergoing tosylation, anhydride formation, and reduction was converted into a key cyclic lactone (Scheme **13**). Subsequent stereoselective electrophilic hydroxylation, iodo-esterification, nucleophilic alkylation, and final deprotection provided (2*S*,3*R*)-AHPA from L-aspartic acid in a 27% overall yield. Key steps here were the highly diastereoselective α-hydroxylation of the lactone and its subsequent opening to the reactive deoxy-iodo- β-homoserine ester.

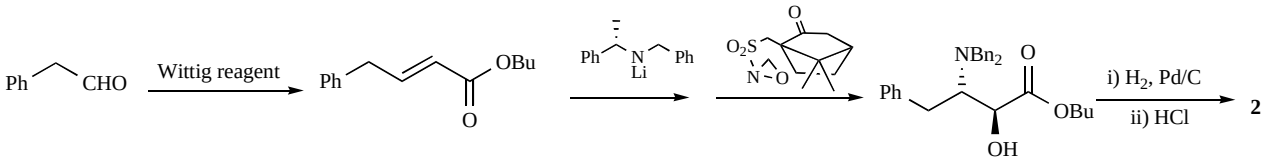
B: Another procedure [34] with L-aspartic acid as the starting material was also introduced; it features formation of the key intermediate oxazolidinone (Scheme **14**). The O-benzylation product was allowed to react with 3-phenyl-2-(phenylsulfonyl)-oxazolidinone (PPSO) to provide the desired chiral alcohol. After hydrogenation, the Cbz-protected product was converted into inverted formate. Birch reduction and hydrogenation yielded **1**. The total yield from L-aspartic acid was less than 10% due to the lengthy process involved. However, other steps were less complex except for the necessary Mitsunobu inversion of the hydroxyl group.



Scheme 14.



Scheme 15.



Scheme 16.

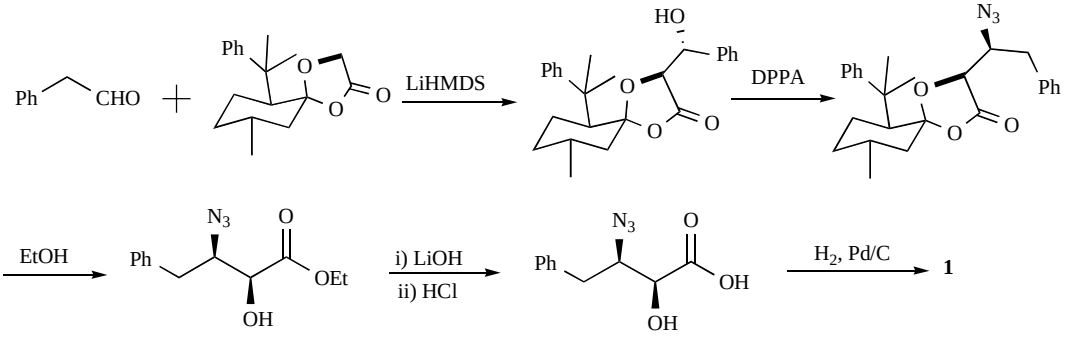
1.4. From Phenylglycolic Acid Derivatives

Several studies have reported using phenylglycolic acid to synthesize AHPAs (Scheme **15**) [35,36]. The methyl ester of phenylglycolic acid reacted with *tert*-butyldimethylsilyl chloride (TBDMSCl) to provide an O-protected product, which was reduced into homologous aldehyde reacting with benzylamine to provide a Schiff base. Subsequent addition, acidic hydrolysis, and ring formation in sequence resulted in a 2-oxazolidone derivative, and (2*S*,3*R*)-AHPA was obtained after a two-step deprotection. Similarly, (2*R*,3*S*)-AHPA can be obtained from methyl-(*R*)-mandelate *via* this method. In this strategy, the optically active imine produced by the condensation of chiral aldehyde with benzylamine contributed to highly stereoselective lactam formation with a 90% chemical yield and 78% *ee*.

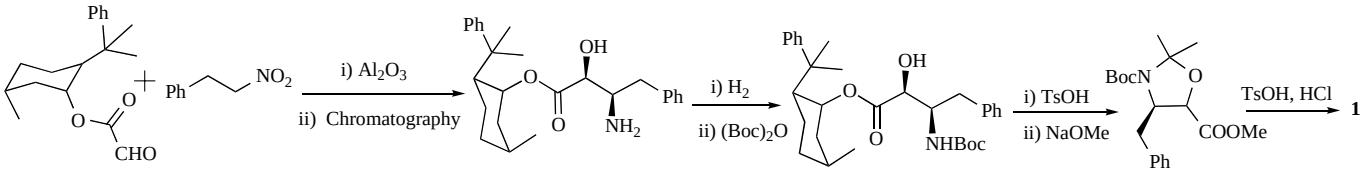
1.5. From Phenylacetaldehyde and its Analogues

A: A new protocol for the synthesis of AHPAs was created by Bunnage *et al.* [37], as shown in Scheme **16**. They started from the reaction of phenylacetaldehyde with Wittig reagents to efficiently provide the corresponding alkene. Tandem conjugate addition-electrophilic hydroxylation of the alkenyl group served to yield the product in required form by introducing (*S*)-(α-methylbenzyl)benzylamide and (+)-(camphor sulfonyl)oxaziridine. Subsequent reactions including debenzylation, hydrolysis, and deionization were used to furnish (2*S*,3*S*)-AHPA with a 39% total yield. In this route, the complementary pairing of homochiral reagents: a,β-amino enolate, and a homochiral oxaziridine, served to guarantee a high stereoselectivity with *anti*:*syn* = 22:1.

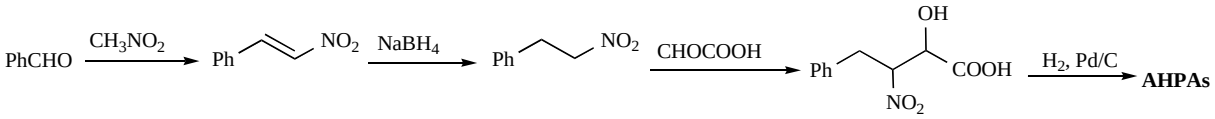
B: William *et al.* [38] achieved the total synthesis of (2*S*,3*R*)-AHPA using a method involving chiral glycolate enolate (Scheme **17**). The enolate of spirocyclic 3-dioxolan-4-one underwent aldol condensation to yield α,β-dihydroxy acid derivative (*anti*:*syn* = 5.7:1). C-3 inversion of the derivative by diphenylphosphoryl azide (DPPA) provided the desired configuration for the target compound. Subsequent reactions were common and easy to accomplish, serving to obtain **1** from phenylacetaldehyde with a 16.7% overall yield. Key features are that the stereochemistry at C-2 was completely controlled by introducing an additional auxiliary group and that the stereo control of C-3 was governed by the choice of enolate counterions, with Li^+ preferring *anti*-aldol.



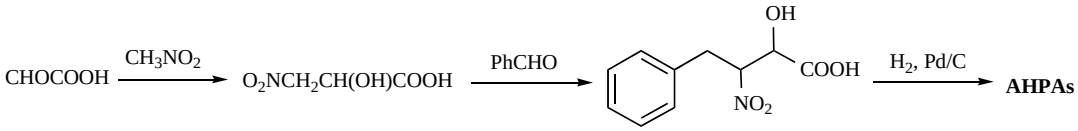
Scheme 17.



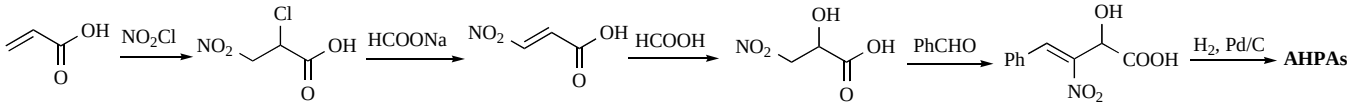
Scheme 18.



Scheme 19.1.



Scheme 19.2.



Scheme 19.3.

C: Jurczak *et al*. [39] also used a chiral auxiliary to achieve better diastereoselectivity from the nitro aldol reaction (Scheme **18**). Diastereomers of the nitro aldol product were separated by flash chromatography to yield a homochiral compound with 42% *de*. The nitro group of this compound was reduced and Boc-protected. The auxiliary portion was then removed in the presence of sodium methoxide and β-amino-α-hydroxy acid was obtained after acidic hydrolysis.

1.6. From Benzaldehyde and its Analogues

The current authors have focused on the total synthesis of AHPBAs, and a new protocol for AHPBAs' synthesis has been developed as a result. Synthesis primarily involves utilizing benzaldehyde, nitromethane, and glyoxalate as main reagents.

A: As shown in Scheme **19.1** [40], nitrophenylethene was furnished by coupling benzaldehyde and nitromethane. With reduction of alkenyl, 2-phenyl-1-nitroethane was readily obtained. Following an addition reaction, the nitro group was transformed into primary amine to provide the expected compound in racemic form with a 14.4% overall yield.

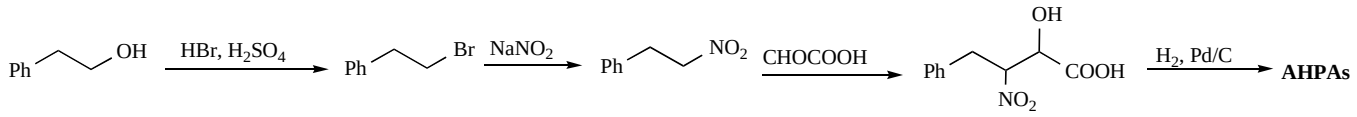
B: In the second route (Scheme **19.2**) [40], the reaction order of these materials was accidentally changed. As a result, AHPBAs were successfully obtained through fewer steps but in a slightly lower yield (11.8%). In this procedure, the glyoxalate was first allowed to react with nitromethane, and the eventual reduction of the nitro group produced by nucleophilic addition accomplished complete synthesis.

C: Another strategy [41] to furnish 2-hydroxy-3-nitropropionic acid was completed through successive chlorination, nitration, elimination, addition, condensation, and hydrogenation with acrylic acid, as shown in Scheme **19.3**. However, this method involved a greater number of steps and failed to improve the overall yield.

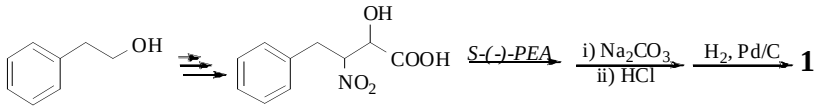
Recently, Liu *et al.* [42] improved this protocol further by allowing nitromethane and benzyl bromide to react directly to provide nitrophenylethane in an 82% yield, which is worth mentioning here and warrants further study.

D: The route of AHPBA synthesis was later modified, as shown in Scheme **20** [43]. It proceeded with successive reactions in the form of bromination, nitration, condensation, and reduction. Compared to the previously described routes [40], this technique is simple, easy, and provides a higher yield of racemate (16.9%).

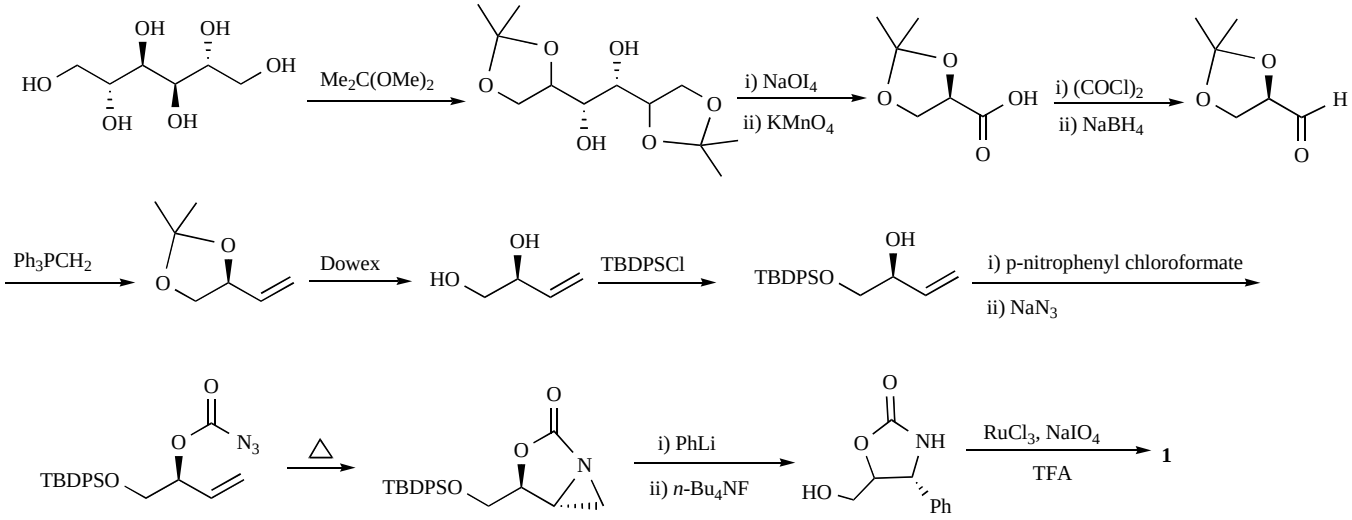
E: In order to both improve the total yield and obtain AHPBA in an optically active form, the current authors have refined methods used in previous studies. One method has proven highly effective (Scheme **21**) [44]. Racemic nitro acids were obtained per the protocol described above [43] and treated with *S*-(-)-



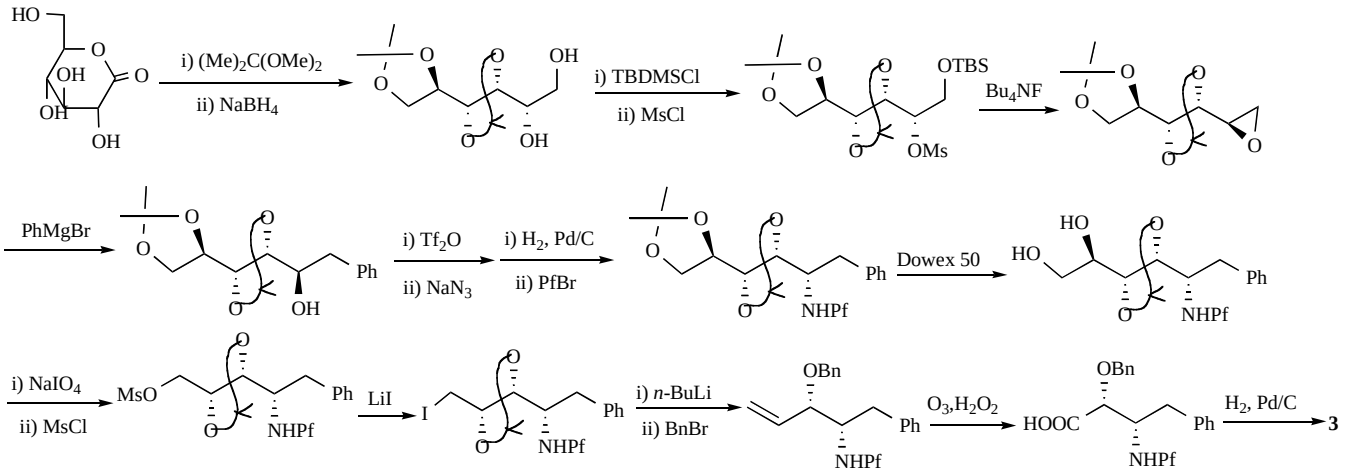
Scheme 20.



Scheme 21.



Scheme 22.



Scheme 23.

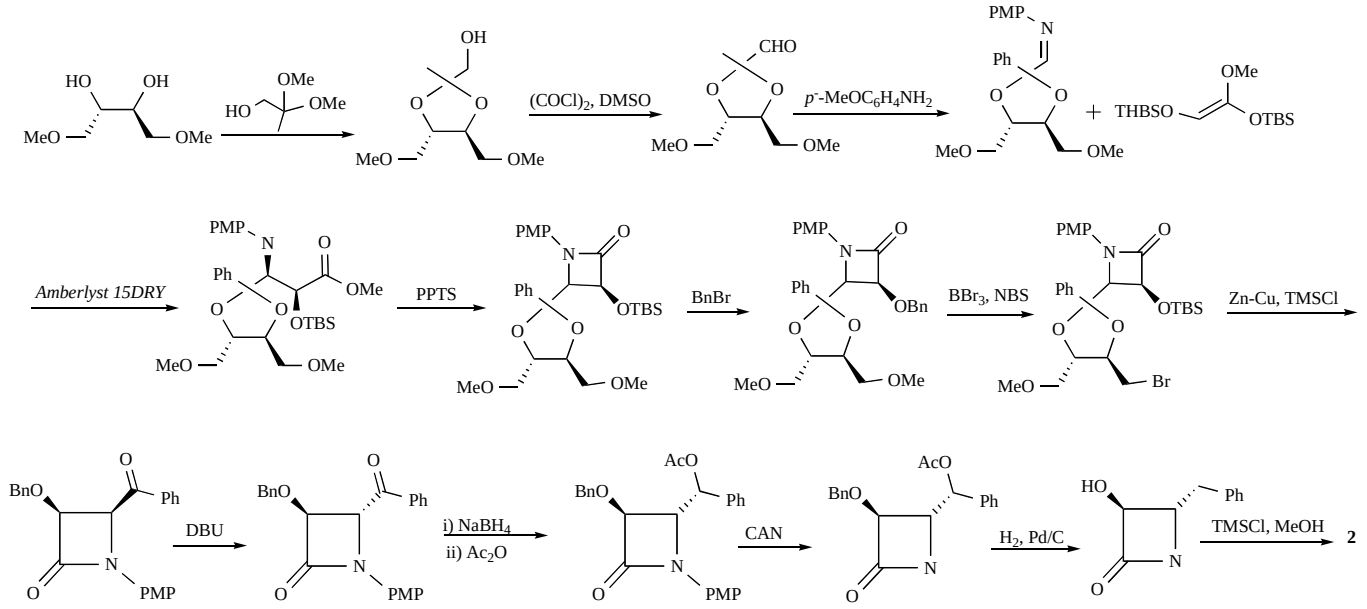
phenylethylamine (*S*-(-)-PEA) to successfully isolate the (2*S*,3*R*)-configuration compound from its enantiomers. The final hydrogenation reaction yielded (2*S*,3*R*)-AHPBA without any racemization of either chiral center.

1.7. From Chiral Sugars

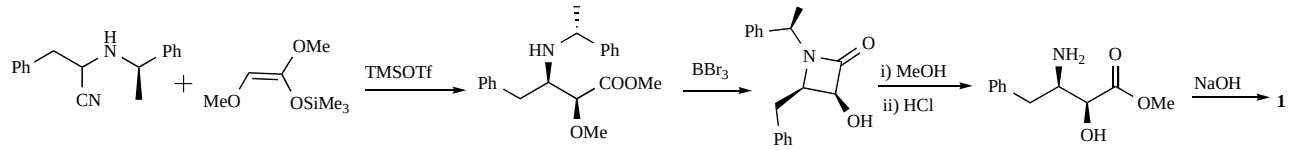
Chiral sugars have also been used to provide the essential chiral centers of AHPA. These substrates are advantageous due to their commercial availability. Nevertheless, achieving proper regioselectivity can be difficult due to the multiple hydroxyl groups in sugars. In addition, such techniques have a low total yield due to a number of steps required.

A: Bergmeier *et al.* [45] (Scheme **22**) began with the protection of mannitol followed by the formation of acid, which was reduced to aldehyde after a Wittig reaction and acidification, to yield allylic alcohol. The monosilylated product mediated by *tert*-butyldiphenylsilyl chloride (TBDPSCl) was converted into hydrazoate in two steps. It was heated to automatically yield aziridine, and oxazolidinone was subsequently formed. This was then oxidized and hydrolyzed to (2*S*,3*R*)-AHPA. This route involves an intramolecular acylnitrene-mediated aziridination strategy to generate a key bicyclic aziridine that determines essential stereochemistry. However, the whole procedure has a total yield of less than 10%.

B: Stereospecific synthesis of (2*R*,3*S*)- and (2*R*,3*R*)-AHPBAs from D-glucono-δ-lactone was also reported by Lee *et al.* [46] (Scheme **23**). They started with the selective silylation of the primary hydroxyl group, following mesylation of the other hydroxyl to



Scheme 24.



Scheme 25.

provide epoxide. A benzyl unit was formed *via* nucleophilic addition. After azidolysis, reduction, and ion exchange chromatography, a diol resulted. Successive oxidation, iodo-substitution, ozonization, and deprotection led to the end of synthesis. In this procedure, the required retention of the C-2 stereochemistry of diol to the corresponding epoxide was accomplished by epoxidation of monomesylate. Furthermore, the same protocol was followed to also obtain (2*S*,3*R*)-AHPA starting from D-gulonic acid-γ-lactone [47].

1.8. From other Synthons

A: A new protocol for synthesizing optically pure (2*S*,3*S*)-AHPA has been introduced [48] depending on a Mannich-type reaction of ketene silyl acetal prepared from (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol [49] with a chiral imine. This results in *syn*-β-amino ester in a good yield with high diastereoselectivity promoted by a cation-exchange resin. This ester is subsequently converted into optically pure β-lactam after a subsequent series of steps, including the removal of the ketal group, epimerization, and inversion of several functional groups, as shown in Scheme **24**. Eventually, the target compound was obtained with no detectable isomerization.

B: Ha *et al.* [50] utilized the chiral precursor 3-phenyl-2-[(*R*)-1-phenylethylamino]propanenitrile as their initial material (Scheme **25**). Reaction of nitrile with trimethylsilyl triflate (TMSOTf) *in situ* yielded a *syn*-product with 68% *de*. The ester was treated with boron tribromide and optically pure lactam was isolated by recrystallization. Subsequent treatment with HCl followed by saponification yielded (2*S*,3*R*)-AHPA. In this method, there are relatively few steps, resulting in a higher overall yield (> 37%). However, the starting material is difficult to obtain and not readily commercially available.

C: According to several studies [51-53], N-[2-oxo-2-(4'-methoxyphenyl)ethyl]acetamide was condensed with glyoxalate to provide 91% enantiomeric acids, which were reduced with hydrogen to yield 92.7% 4-deoxy-product (Scheme **26**). This was then treated with optically pure *S*-(-)-1-phenylethylamine to predominantly form a (2*S*,3*R*)-acid amine salt. The acid was subsequently liberated with sodium hydrate, which was deacetylated by acidic hydrolysis to yield a (2*S*,3*R*)-AHPA derivative. This method involves use of an exotic optically active substance to obtain the desired stereochemistry but is relatively more convenient.

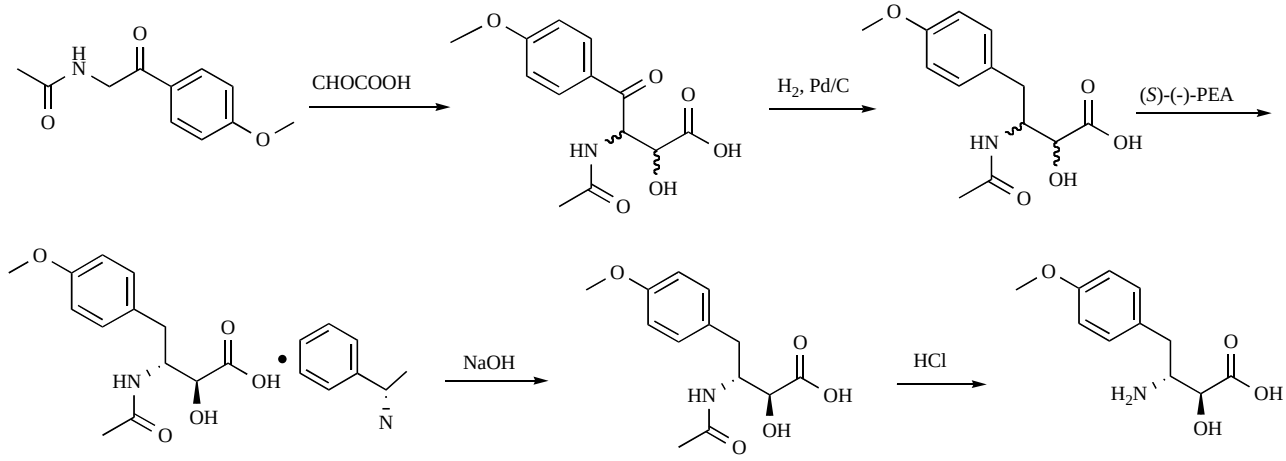
2. INTRODUCING SPECIAL CATALYSTS

Several stereoselective synthetic strategies have also been developed. These strategies can be classified into several groups according to the methods they use, like stereoselective reduction, epoxidation, cycloaddition of imines, and ketene acetals. Strategies that are mainly discussed here are epoxidation and other strategies that have made marked progress.

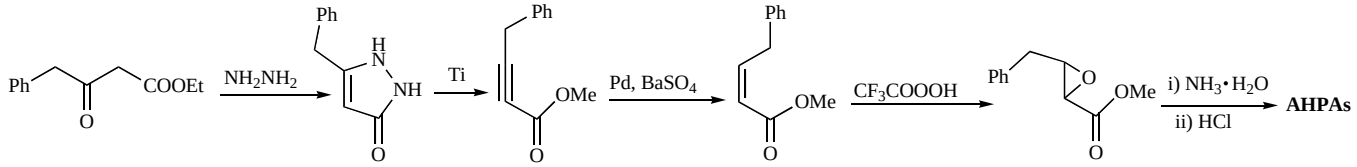
2.1. Through Epoxidation

A: Synthesis of AHPAs by epoxidation was first put forth by Takita *et al.* [54] and is shown in Scheme **27**. Phenylethyl acetoacetate reacted with hydrazine and the product was dehydrogenated in the presence of titanium to provide an alkynyl group, which was subsequently reduced with a Lindlar catalyst. The process of obtaining epoxide was mediated by peroxide, the ring of which was opened by aminolysis, and final acidification yielded the target compound. Unfortunately, this method results in poor stereo- and regioselectivity and only obtains a racemate, although isomers can be separated with some difficulty.

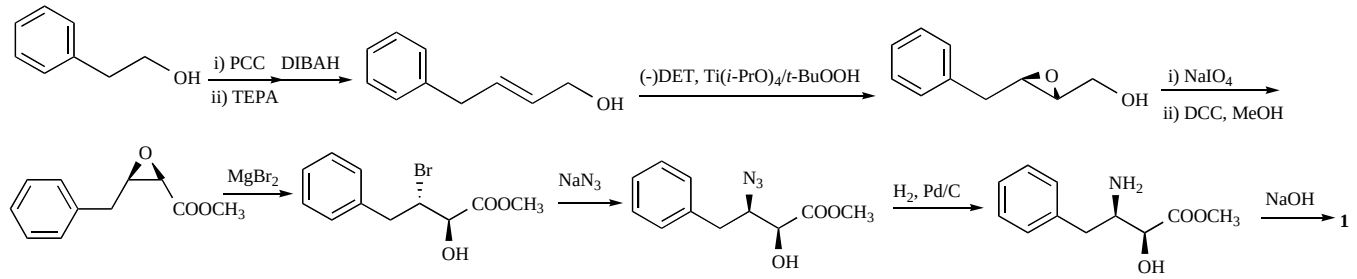
B: Comparing traditional Sharpless asymmetric epoxidation [55] with direct aminohydroxylation, Righi *et al.* [1,56] determined that the former allowed a more flexible access to a larger variety of diastereoisomers despite more steps required for the transformation of epoxy alcohols into final amino alcohols, so they designed the route of synthesis shown in Scheme **28.1**. Starting with commercially available alcohol, allylic alcohol was produced by successive oxidation, standard two-carbon homologation, and **c**hemoselective



Scheme 26.



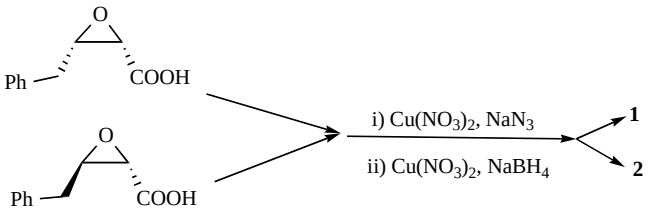
Scheme 27.



Scheme 28.1.

reduction with diisobutylaluminum hydride (DIBAL). Epoxy alcohol was yielded by classic asymmetric epoxidation. The $MgBr_2$-mediated opening of epoxy provided *anti*-bromohydrin in a nearly quantitative yield (92%), and the subsequent substitution of azide for halogen yielded vicinal azido alcohol with a *syn* relationship between the two chiral centers, a feat that was difficult to accomplish with other approaches.

Francesco *et al*. [57] further developed one-pot copper-catalyzed synthesis of α-hydroxy-β-amino acids by azidolysis of α,β-epoxycarboxylic acids and the subsequent reduction of the resulting intermediate (Scheme **28.2**). AHPAs in pure form were isolated by simple ion-exchange resin purification, providing (2*S*,3*R*)-AHPBA and (2*S*,3*S*)-AHPBA in a 75% yield with 95% *ee* and in a 72% yield with 90% *ee*, respectively.

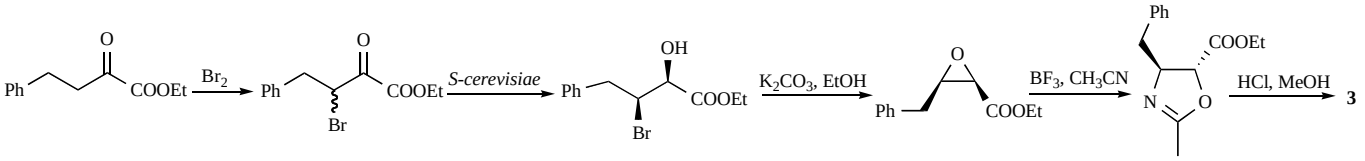


Scheme 28.2.

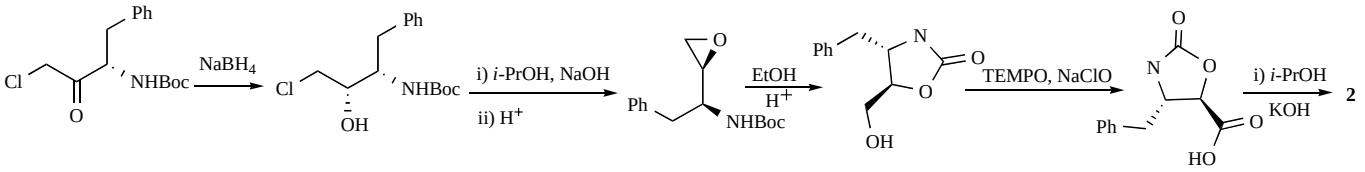
C: A highly enantioselective route to 3-amino-2-hydroxy acids by biocatalytically asymmetric reduction was also developed [58]. As shown in Scheme **29**, synthesis began with the bromination of α-ketoester, followed by bioreduction using *Saccharomyces cerevisiae*, obtaining *syn*-ester selectively with 96% *ee*. The subsequent epoxide was transformed into oxazoline and finally opened by acidic hydrolysis to provide (2*R*,3*S*)-AHPA in an exceptional yield and with a high *ee*. In this strategy, the epoxide intermediate and the oxazoline intermediate synergetically shorten the whole process and guarantee exceptional stereoselectivity.

D: Another practical means [59] of obtaining AHPAs through the key intermediate oxazolidine-2-one derivative was developed (Scheme **30**), the specific reaction conditions of which are shown below. The key step is the reaction of Boc-protected β-amino epoxide with an acid to provide stereospecific 5-hydroxymethyl oxazolidine-2-one, which was oxidized in the presence of TEMPO and hypochlorite to predominantly yield an *anti*-oxazolidine carboxylic acid followed by opening of the ring of oxazolidinone.

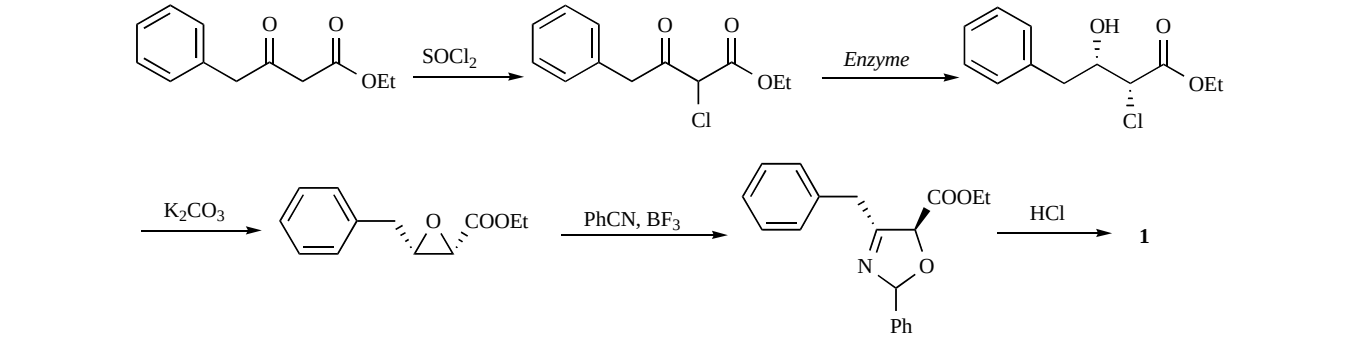
E: Bakers' yeast reductase was used in the strategy shown in Scheme **31** [60], which helped to transform chloroketone into (2*R*,3*S*)- chlorohydrin in > 98% *ee* and > 98% *de*. *Cis*-glycidate was yielded by the treatment of K_2CO_3 followed by the opening of epoxy in the presence of benzonitrile with no C-3 epimerization. Since C-3 was secondary, this procedure presumably promoted a tighter association of the nitrogen nucleophile. Acidic hydrolysis proceeded uneventfully to provide (2*S*,3*R*)-AHPA from β-keto ester in a 48% total yield.



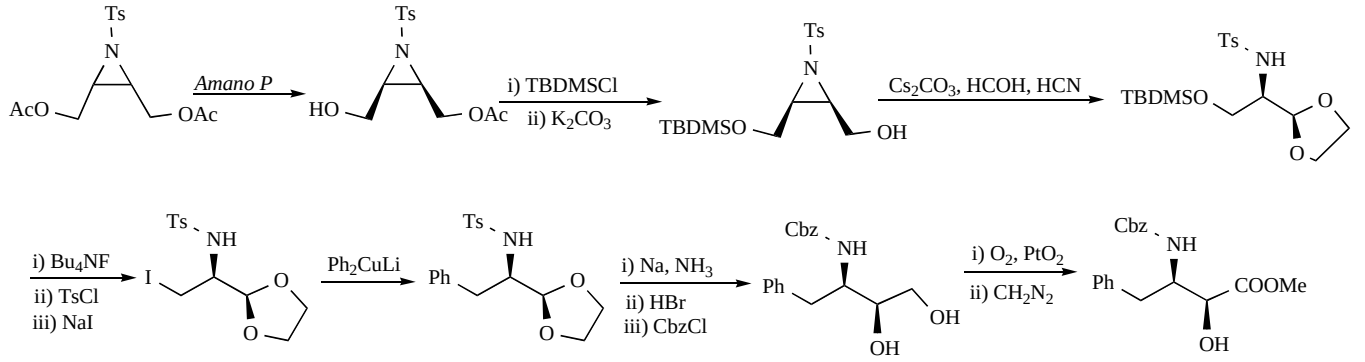
Scheme 29.



Scheme 30.



Scheme 31.



Scheme 32.

2.2. Through Non-Epoxidation

Some asymmetric catalysts like enzymes or inorganic ligands have been used to promote the transformation of prochiral starting materials with specific structures into expected chiral compounds. Such techniques offer the promise of synthesizing optically active AHPBAs with high stereoselectivity.

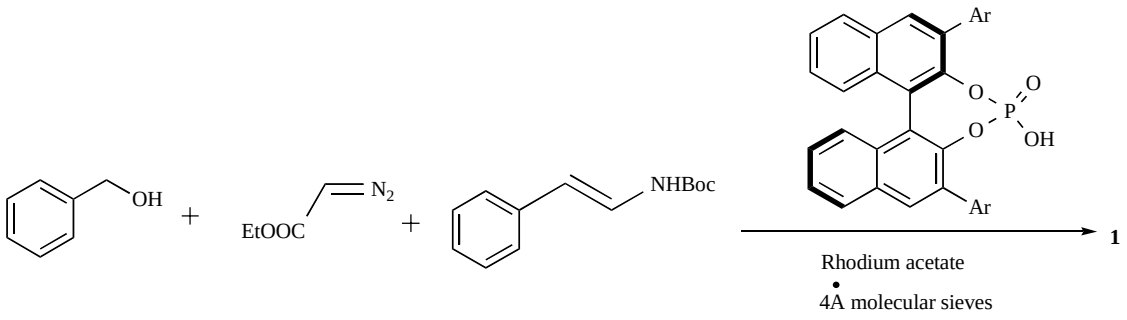
A: Fuji *et al.* [61] (Scheme **32**) began their synthesis with the enzymatic transesterification of aziridine to alcohol, which selectively yielded (2*R*,3*S*)-product with 95% *ee*. The subsequent silylation reaction, ring opening reaction, and iodo-substitution yielded iodide followed by the formation of a phenyl unit. The new Cbz-protected diol was oxidized and methylated, resulting in a (2*S*,3*R*)-AHPBA derivative from optically active aziridine in a 34% total yield.

B: Recently, great strides have been made in increasing the total yield of AHPAs by shortening the route of their synthesis and utilizing efficient catalysts [62]. As shown in Scheme **33**, the multicomponent reaction of a diazo compound, alcohol, and styrylamine derivative under catalysis of a chiral phosphoric acid derivative and rhodium acetate with molecular sieves as activators predominantly produced (2*S*,3*R*)-AHPA. Final purification with column chromatography provided **1** in pure form with a 60% yield and 70% *ee*. Presumably, the high diastereoselectivity is due to the exceptional selectivity of both catalysts and the strong activation effect of molecular sieves.

CONCLUSION

Optically pure β-amino-α-hydroxyphenylbutanoic acids, key intermediates for numerous organic substances, have served as templates for peptide isosteres and are constituents of several natural products that have potent biological activities like the immunoregulatory drug Bestatin, HIV protease inhibitors KNI-272, and several renin inhibitors. Clearly, AHPAs are of critical importance in pharmaceutics. This review thus discussed numerous ways of synthesizing AHPAs, and particularly strategies used to obtain AHPAs in optically active forms, in order to provide a convenient means of understanding the basics of this field.

Determining and comparing the specific strategies leads to the reasonable conclusion that a strategy utilizing some commercially



Scheme 33.

available chiral synthons, including those of amino acids and sugars, is the most common and convenient means of achieving the total synthesis of AHPAs. However, a serious drawback to this strategy is that the lengthy process leads to low overall yield. Fortunately, moves like the introduction of bulky auxiliaries and use of efficient catalysts have markedly improved total efficiency. That said, such functional materials are relatively hard to obtain and quite expensive. Thus, a combination of several strategies, like the coordination of economical chiral starting materials and efficient obtainable catalysts, may lead to an economical, efficient, and large-scale route to synthesize the versatile structure of these acids. Such approaches will, however, require a great deal more study.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

AHPA	=	3-amino-2-hydroxy-4-phenylbutyric acid
APN	=	aminopeptidase N
DIBAH	=	diisobutylaluminum hydride
DCC	=	1,3-dicyclohexylcarbodiimide
DMAP	=	4-dimethylaminopyridine
CDI	=	N,N'-carbonyldiimidazole
DMSO	=	dimethylsulfoxide
DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
TEMPO	=	2,2,6,6-tetramethylpiperidine-1-oxyl radical
NMM	=	4-methyl-4-morpholine
MoOPH	=	molybdenum oxide pyridinium hexamethyl phosphoramide complex
CSA	=	camphorsulphonic acid
TFA	=	trifluoroacetic acid
BINAP	=	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Pf	=	9-phenylfluoren-9-yl
EEDQ	=	IV-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
LDA	=	diisopropylamide
LHMDS	=	hexamethyldisilazide
TFAA	=	trifluoroacetic anhydride
DPPA	=	diphenylphosphoryl azide
TEA	=	triethylamine
DME	=	1,2-dimethoxyethane
PPSO	=	3-phenyl-2-(phenylsulfonyl)-oxazolidinone
DEAD	=	diethylazodicarboxylate
TBDMSCl	=	*tert*-butyldimethylsilyl chloride
LiHMDS	=	lithium hexamethyldisilazide
S-(-)-PEA	=	*S*-(-)-phenylethylamine
TBDPSCl	=	*tert*-butyldiphenylsilyl chloride
Tf	=	trifluoromethanesulfonyl
PPTS	=	pyridinium p-toluenesulfonate
NBS	=	N-bromosuccinimide
TMSOTf	=	trimethylsilyl triflate
CAN	=	ceric (IV)-ammonium nitrate
PCC	=	pyridinium chlorochromate
DET	=	diethyl tartrate
TEPA	=	tetraethylenepentamine

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