Chapter 13

Approaches to the Asymmetric Synthesis of Unusual Amino Acids

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1. Introduction

This chapter will focus on critically evaluating some selected new methods to achieve the asymmetric synthesis of α-amino acids. It is not meant to be comprehensive, but rather to reflect some of the possibilities opening up in this area.

The study of α-amino acids is one of fundamental importance to many areas of chemistry and its relation to molecular biology. Nature only utilizes 20 amino acids in the production of polypeptides on genes, yet the combinations of these amino acids have provided a wonderful diversity of chemical structures and functions. The number of naturally occurring or synthetically derived nonproteogenic α-amino acids is rapidly increasing and, depending on definitions, might already have exceeded 1000. In addition, because of the significant advances in the technology of synthesizing polypeptides (e.g., the solid-phase Merrifield method), the possibilities in the design and synthesis of new enzymes, hormones, synthetic immunostimulants, drugs, and countless other important biopolymers have been dramatically increased. Certain nonproteogenic amino acids have already proven of considerable experimental value in probing amino acid chemistry and function, as a tool for enhanced understanding of the roles and functions of proteins, in understanding the chemistry and biochemistry of interactions in living systems, and as analogs of naturally occurring hormones, neurotransmitters, growth factors, enzyme inhibitors, neuromodulation, immunomodulators, and many other biologically significant compounds.

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In the past several years, the asymmetric synthesis of α-amino acids and their derivatives has become a highly active area of research, and several reviews have appeared on the chemistry and biochemistry of α-amino acids and their uses. In 1988 and 1989, two important reviews and discussions on asymmetric synthesis of α-amino acids appeared *(1,2)* Both were extensive and well organized. Hence, this chapter will cover primarily studies since that time with special emphasis on α-amino acids that can be used in the design of conformationally and topographically constrained peptides.

2. Synthetic Methods

Since so many methodologies have been established for the asymmetric α-amino acids synthesis, it often is difficult to select the most appropriate methodology for constructing the amino acid of immediate interest. Thus far, despite all the methodologies available, there is no one single best method that a laboratory may use to solve every amino acid problem that may be encountered. In a recent report *(3)* Schmidt et al. summarized four general methodologies used for the preparation of optically active, nonribosomal α-amino acids and α-alkylamino acids:

1. Alkylation or amination of optically active enolates;
2. Alkylations with optically active, electrophilic glycine compounds;
3. Diastereoselective Strecker and Ugi reactions with optically active amines; and
4. Diastereoselective hydrogenation of α, β-dehydroamino acid derivatives.

Except for the last method, nearly all of the above processes give rise predominantly or exclusively to compounds in either the *S*- or the *R*-series. In these cases, the enantiomer often is considerably more difficult to obtain because usually only one of the two enantiomers of the optically active auxiliary reagent employed (amino acids, amino alcohols) is "cheaply" available. Meanwhile, numerous miscellaneous methods have been developed, some of which are very efficient and show excellent control of both stereochemistry and regiochemistry. Biologically related methods also are very attractive these days. Enzymatic, chemoenzymatic, and cell-free biosynthesis of nonproteinogenic α-amino acids has shown good results *(4–9)*. Since the α-amino acids generally are not the final goal of the research, it often is important that the method is amenable to rapid implementation.

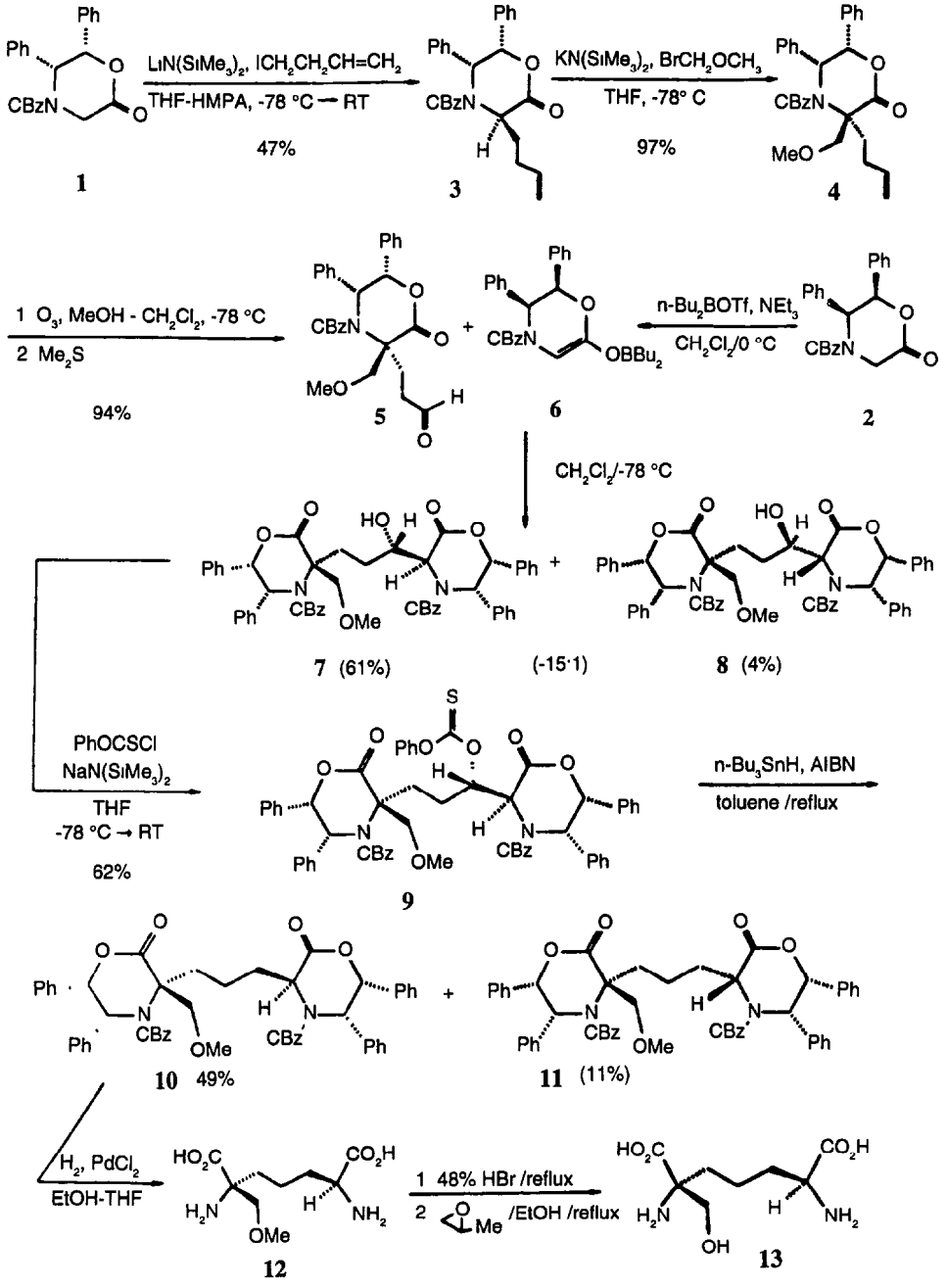
3. Syntheses of α-Amino Acids

3.1. Asymmetric Derivatization of Glycine and Other Proteogenic α-Amino Acids

Derivatization of glycine is one of the most frequently used approaches for the preparation of α-amino acids. Since glycine is the simplest amino acid, derivatization of glycine (including "double derivatization" to make α, α'-disubstituted α-amino acids) can, in principle, provide an infinite variety of α-amino acids. Numerous approaches have been devised and previously reviewed *(1–3)*. Here, we will focus on the work that has been done during the past 3 yr.

Williams' group has been a leader in this area with the development of several specific methodologies *(10)*. Most recently, Williams and associates reported an asymmetric synthesis of 2,6-diamino-6-(hydroxymethyl) pimelic acid using this approach *(11)*. (5R, 6S)-4- (benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**1**) underwent electrophilic alkylation to give the allyoxazinone **3** (Scheme 1), which then underwent another electrophilic alkylation at the same position to give the (methoxymethyl)homoallyoxazinone **4** in high yield. The adduct **4** was ozonolized to aldehyde **5**, which was coupled with enolate **6** prepared from the enatiomer of starting material **1** (5S, 6R)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-1,4-oxazin-2-one (**2**). The enantioselectivity is good (Scheme 1). After separation, the major product of coupling reaction, **7**, was treated with phenyl chlorothionoformate along with bis (trimethylsilyl) amide to give the thionoformate **9**. Reduction of **9** provided the product **10** (and **11**; some racemization occurred in this step). After separation, the dilactone **10** was hydrogenated to give the amino acid **12**, which was then directly converted into (2S, 6R)-2,6-diamino-6-(hydroxymethyl)pimelic acid **13**. (2S, 6S)-**13** also was synthesized by the same protocol, starting with **2**; the diastereoselectivities was better in the latter case.

Based on their experiences *(12)*, Belokon and associates recently reported an asymmetric synthesis of a series of α-amino acids via alkylation of the chiral nickel(II) Schiff base complex of glycine and alanine *(13)*. The overall yield of the reaction is good, but the diastereoselectivity is not high. At about the same time, they also reported another asymmetric synthesis of 4-substituted proline derivative via condensation of "Glycine" with olefins *(14)*. The "Glycine" here is a chiral Ni(II) complex of


LiN(SiMe3)2, ICH2CH2CH=CH2
THF-HMPA, -78 °C → RT
47%
KN(SiMe3)2, BrCH2OCH3
THF, -78° C
97%
1 O3, MeOH - CH2Cl2, -78 °C
2 Me2S
94%
n-Bu2BOTf, NEt3
CH2Cl2/0 °C
CH2Cl2/-78 °C
7 (61%)
(-15·1)
8 (4%)
PhOCSCl
NaN(SiMe3)2
THF
-78 °C → RT
62%
n-Bu3SnH, AIBN
toluene /reflux
10 49%
11 (11%)
H2, PdCl2
EtOH-THF
1 48% HBr /reflux
2 /EtOH /reflux

Scheme 1.

glycine. The diastereoselectivity at C_α (90%) and C_β is high. Nebel and Mutter reported a stereoselective synthesis of isovaline (IVA) and IVA-containing dipeptides *(15)*. The starting material, which acts as the chiral inducer, is a methylated glycine chiral template (oxazolidinone derivative). The key step is the alkylation of the α-position of an α-methylated glycine template under basic condition. The synthetic route is only three steps and provided isovaline with high yield along with high diastereoselectivity (>99%). Guanti and associates synthesized β-hydroxy-α-amino acids by utilizing dibenzylaminoacetates as synthetic equivalents of glycine *(16)*. The starting dibenzylaminoacetates were treated with LDA to afford lithium enolates and, following acidic aldol condensation with silyl ketene acetals, yielded predominant *syn* adducts with selectivity from 5:1 to 32:1. The best results (in terms of yields and stereoselectivity) were from an acylation–reduction process (aldol reaction with an acid chloride). The selectivity of the *syn* isomer was >13:1. Dellaria and Santarsiero *(17)* reported the enantioselective synthesis of α-amino acids derivatives via stereoselective alkylation of a homochiral glycine enolate. A simple one-pot, three-step deprotection provided the final α-alkylated glycine.

Schollkopf's group has been one of the pioneers in this area *(18,19)*. Recently, they reported a new asymmetric synthesis of (2R, 3S)-*threo*-3-arylserine derivatives *(20)*, using a titanium derivative of the bislactim ether of *cyclo*(-L-Val-Gly) as a chiral template. Simple hydrolysis afforded (2R, 3S)-*threo*-arylserine methyl ester. Mittendorf and Hartwig *(21)* reported a synthesis of 2,3-diamino acids using bislactim ethers (Schollkopf-type glycine enolates) as chiral auxiliary to achieve asymmetric α-alkylation (from 84 to >95%). The electrophile they used for alkylation was dibromomethane. Another key step in their synthesis was the azide displacement to the product (the bromide) of asymmetric alkylation in order to obtain the three-amino functionality. Very recently, Hamon and associates reported a very interesting way to derivatize glycine *(22)*. The chiral auxiliary they used was (–)-8-phenylmenthol. The key reaction is the asymmetric alkylation of the 8-phenylmenthyl ester of the N^α-Boc derivative of 2-bromoglycine by treatment with allyl-*tri-n*-butylstannanes. The diasteroselectivity is excellent.

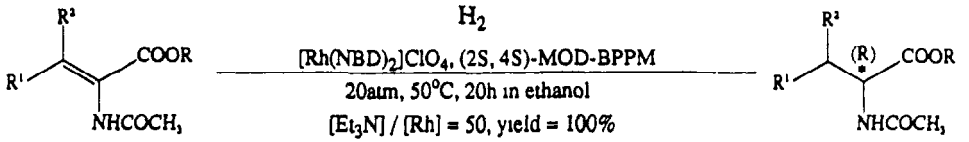
Seebach's group is also one of the leaders in this area *(23,24)*. Recently, they reported a stereoselective synthesis of MeBmt by employ-

ing a new chiral glycine enolate derivative that is a chiral oxazolidineones derivative *(25)*. The electrophile they used for asymmetric alkylation was (2R, 4E)-2-methyl-4-hexenal. This aldol addition reaction was complicated and gave an unexpected product. The diastereoselectivity is good at the reaction center, but the yield of the major product was not excellent, even though MeBmt was obtained with a reasonable overall yield of 30–39% in a four-step process.

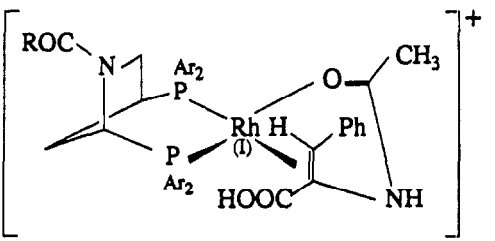
3.2. Asymmetric Hydrogenation Method

Asymmetric hydrogenation is one of the major methodologies for the synthesis of amino acids. The substrates of this type of hydrogenation usually are Schiff's bases *(9)* or α,β-unsaturated derivatives (dehydro-α-amino acids). The catalysts of this type of hydrogenation usually are chiral rhodium complexes. Because this methodology can provide a short and efficient route to various amino acids, it is very attractive to the industry, and a lot of this work has been patented. Several recent notable applications of this technology are worthy of note.

Takahashi and Achiwa reported the synthesis of a series of α-amino acid derivatives via asymmetric hydrogenation of (*Z*)-2-acetamidoarylic acid derivatives *(26)*. The catalyst they used was (2S, 4S)-MOD-BPPM rhodium complex. The reaction and proposed mechanism are shown in Scheme 2. In this case, the α-amino acids have the *R* configuration, and reasonably high e.e. values (58.6–98%, varies from substrate) were obtained. Shioiri and associates reported a synthesis of derivatives of β-hydroxy-α-amino acids *(27)*. They used different starting materials to synthesize 4-alkoxycarbonyloxazole derivatives, which are synthons for β-hydroxy-α-amino acids. The 4-alkoxycarbonyloxazole can undergo rearrangement under acidic conditions to give 5-substituted 3-amino-tetronic acid. This α,β-unsaturated acid was treated with 5% rhodium-alumina in ethyl acetate at 120 atm and ambient temperature for 24 h to afford the optically active 5-substituted lyxo-1,4-lactone. Both the diastereoselectivity and the yield of the reaction are high. In the same paper, they also reported the asymmetric transformation of α-amino acids to related β-amino acids. Gladiali and Pinna reported a synthesis of (–)-(R)-α-methylserine via a regioselective hydroformation *(28)*. The starting material they used was methyl *N*-acetamidoarylate (MAA). It was treated with CO/H_2 (1:1) at 80°C, 100 atm for 70 h with the catalyst of $HRd(CO)(PPh_3)_3$/chelating diphosphine to afford an α-amino alde-



(2S, 4S)-MOD-BPPM: (2S, 4S)-N-(ᵗButoxy-carbonyl)-4-{[bis(4'-methoxy-3',5'-dimethylphenyl)]phosphino}-2-{[[bis(4'-methoxy-3',5'-dimethylphenyl)]phosphino]methyl}pyrrolidine



Transition State of the Asymmetric Hydrogenation

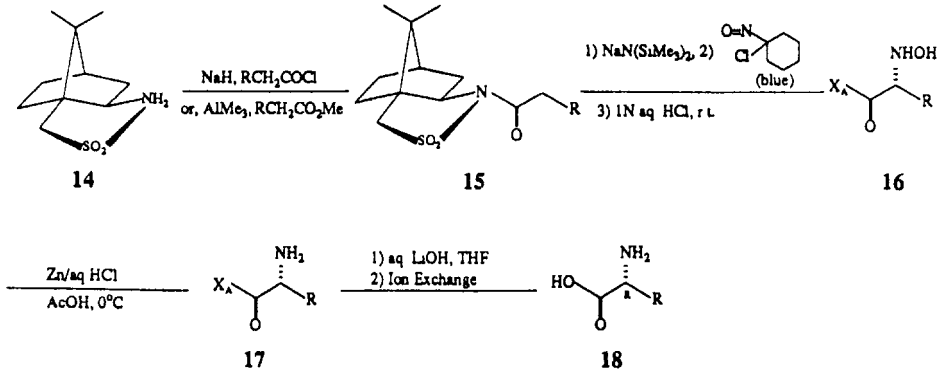
Scheme 2.

hyde. The diastereoselectivity of the reaction is >9:1 whereas the enantiomeric excess is <60%. The aldehyde obtained underwent reduction to provide (–)-(R)-α-methylserine. Very recently, Genet and associates reported a "practical production" of D- and L-threonine *(29)*. They started with a derivative of 3-oxobutyrate. After electrophilic amination, they obtained an oxime (Schiff's base type) that underwent normal catalytic hydrogenation to afford 2-racemic α-amino-3-oxobutyrate. This 2-acylamino-3-oxobutyrate was reduced to β-hydroxy α-amino acid derivatives through a dynamic kinetic resolution in rhodium- and ruthenium-catalyzed hydrogenation. The results and the reaction mechanisms of the hydrogenation by utilizing these two catalysts have been compared. It appears that the hydrogenation with the catalyst of chiral biphosphine ruthenium complex provides better results. Schmidt et al. have reported the synthesis of the derivatives of trihydroxynorleucines [(2S,4S,5S)- and (2R,4S,5S)-2-amino-4,5,6-trihydroxyhexanoic acid] *(30)*. Starting with the corresponding α,β-didehydro compounds, they used the optically active homogeneous catalyst $[Rh(COD)(DIPAMP)]^+BF^-$

to realize the asymmetric hydrogenation and obtained the protected α-amino acids.

3.3. Nucleophilic Amination of α-Substituted Acids and Electrophilic Amination of Enolates

These two approaches have been attractive to chemists, because they can provide highly selective asymmetric synthesis of α-amino acids and can be used to obtain important unusual amino acids. The general ideas of these strategies are quite straightforward. Nucleophilic amination involves an S_N2 reaction between an α-substituted acid or its precursor and an amino nucleophile. Usually the substituents at the optically active α position of the acids (or precursors) are halogens or hydroxyl groups. The nucleophile can vary, as will be seen in the following examples. The idea of electrophilic amination of enolates involves the reaction of an enolate with a nitrogen-centered electrophile. The stereochemistry is usually controlled by the neighboring chiral auxiliary or the neighboring chiral centers. Because of the nature of nitrogen atoms, it is hard to make an electrophilic nitrogen. Although considerable effort has been made already, much more is needed. Indeed thus far, the only highly successful electrophilic amination appears in nature. Oppolzer's group has been one of the leading groups working on both electrophilic amination of enolates and nucleophilic amination of α-substituted acid derivatives *(31)*. Recently, Oppolzer and Tamura reported the asymmetric synthesis of α-amino acids via electrophilic amination *(32)*. They used a new chiral sultam **14** (Scheme 3) as a chiral auxiliary. They coupled **14** with an acid chloride to give **15**, in which R corresponds to the carbon skeleton of the desired amino acids. The hydroxylamine **16** was obtained via electrophilic amination by treating **15** with an electrophilic nitrosochloride (the nitrosochloride also acts as an indicator of the reaction). The aminations were shown to give ca. 100% selectivity within the limits of ^{1}H-NMR analysis. The hydroxyl amine **16** was reduced to the amine **17**, followed by removal of the chiral auxiliary and basic hydrolysis to give (R)-α-amino acids **18**. (S)-α-amino acids **(18)** are equally accessible by using the available antipode of auxiliary **14** (entries b and i in Table 1). The synthesis is highly stereoselective with high yields, and can provide a variety of pure (R)- and (S)-α-amino acids. In the same paper, they also reported an interesting route for the synthesis of β-chiral α-amino acids as shown in Scheme 4. The two chiral centers in hydroxylamine **20** were



14 15 16 17 18

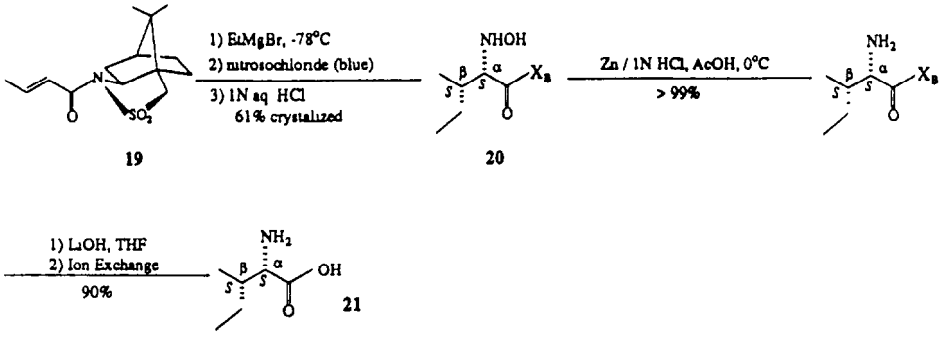
Scheme 3.

Table 1
Transformation of *N*-Acylbornylsultams
into Enantiomerically Pure α-Amino Acids **18**

	R	Yield% 16	Yield% 17	Amino acids	Yield%	e.e.%	Config.
a	CH_3	80	83	**18**	>99	>99	R
b	CH_3	82	78	**(S) - 18**	99	>99	S
c	CH_2=CH—CH_2	69	78	**18**	>99	>99	R
d	Me_2CH	70	85	**18**	>99	>99	R
e	Me_2CH—CH_2	87	97	**18**	>99	99	R
f	$PhCH_2$	78	93	**18**	94	>99	R
g	Ph	77	95	**18**	97	>99	R
h	*p*-MeOph	72	84	**18**	97	>99	R
i	*p*-MeOPh	73	90	**(S) - 18**	99	>99	S

generated via addition of *N*-crotonoylsultam **19** by a nucleophile (ethylmagnesium bromide) or by an electrophile (the nitrosochloride). This step was achieved with high stereoselectivity (99% e.e. at C[α], 90% e.e. at C[β]). The conditions of converting the hydroxylamine **20** to an α-amino acid are the same as in Scheme 3. They ended up with (S,S)-isoleucine **21**.

Takano and associates reported a concise route for synthesis of (S)-phenylalanine *(33)*. They used (R)-epichlorohydrin as starting material. Optically active epoxides often have been used as building blocks in the synthesis of β- or γ-hydroxy α-amino acids. After lengthening the car-



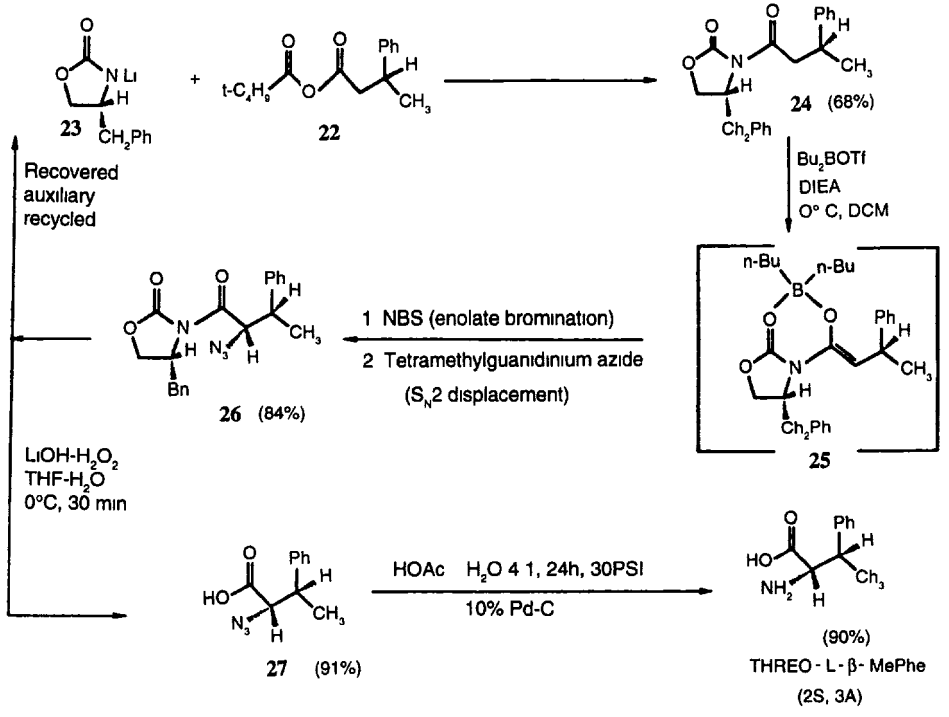
Scheme 4.

bon backbone, they obtained an internal acetyl that has an allylic hydroxyl group. The hydroxyl group was replaced by the treatment with phthalimide under basic conditions. The inversion of chirality at the reaction center is expected. The adduct then underwent reduction, oxidation (to acid), and finally deprotection to afford (S)-phenylalanine. Jung and Jung reported a "rapid" synthesis of β-hydroxy-α-amino acids *(34)*. They started with an allylic alcohol that underwent Sharpless asymmetric resolution to provide optically active alcohols as key intermediates. The nucleophilic amination was achieved by treating the epoxide with benzoyl isocyanate. The adduct was treated with NaH to obtain optically active oxazolidinones. Following oxidation of the hydroxy group, opening of the oxazolidinone ring provided L-threonine, β-hydroxyphenylalanine, or β-hydroxyleucine depending on the reagents used. Schmidt and associates prepared α-amino-β-hydroxy acids by using nucleophilic amination *(3)*. They started with an allylic alcohol that underwent Sharpless oxidation. The epoxide alcohol obtained was converted to an imide ester in excellent yield by treatment with tricholoroacetonitrile/DBU. The imide nitrogen then underwent regioselective intramolecular nucleophilic attack to open the epoxide ring. The oxazolines were converted to oxazolidinones that underwent Jones' oxidation, hydrolysis, and deprotection to afford *N*-Boc-α-amino-β-hydroxy acid esters. The stereochemistry was well controlled by Sharpless asymmetric epoxidation. Wagner and associates also reported a synthesis of a β-hydroxy α-amino acid *(35)*. They started with (R,R)-(+)-tartaric acid. After regioselective protection, they obtained a triflate (C-2) with all other functionalities protected by benzyl groups. The triflate was exposed

to tetramethylguandinium azide to afford an azide that underwent reduction. A series of regioselective deprotection and reprotection steps provided N^{α}-Boc-(2S,3R)-3-hydroxy aspartic acid. Evans' group is one of the leading groups in this area. They have done outstanding work on nucleophilic amination and electrophilic amination of enolates using the same chiral auxiliary *(36)*, and in a recent paper have summarized this work *(37)*. They did the nucleophilic amination through an azide displacement with a chiral bromide (S_N2 mechanism). The diastereoselectivity of the former bromination depends on the reagent used to make the enolates. They also have examined direct azidation to the enolates. The selection of quenching reagent for this reaction is critical. They achieved both high yield and protection from racemization by using glacial acetic acid at low temperature for quenching. Recently, in our own laboratory, we have synthesized several β-methyl α-amino acid analogs. Using in part Evans' methodology *(38–41)* asymmetric synthesis of all four isomers of β-methylphenylalanine *(42)* (Scheme 5) was achieved. We used *S*-(+)-3-phenylbutyric acid **22** as starting material, which was attached to the chiral auxiliary **23** derived from D-phenylalanine to afford *N*-acyl oxazolidinone **24**. Oxazolidinone **24** was converted to a boron enolate **25** by use of dibutylborontriflate in dichloromethane. Stereoselective bromination was accomplished using NBS, and S_N2 displacement of the resulting crude bromide by tetramethylguanidium azide gave the diastereoisomeric azide **26** with high stereoselectivity (Table 2). Removal of the chiral auxiliary was effected by hydrolysis using LiOH in the presence of hydrogen peroxide, followed by reduction (10% Pd-C, 1:1 AcOH:H_2O) of the resulting azido acid **27** which gave *threo*-L-β-methylphenylalanine. We provide here the details of the asymmetric synthesis of a β-methylphenylalanine.

3.3.1. General Procedure for the Preparation of N*-Acyloxazolidinone: Illustrated by the Preparation of (4R)-3-(3'S)-3'-(Phenylbutanoyl)-4-(Phenylmethyl)-2-Oxazolidinone,* ***24*** (42)

1. To a stirred solution of 19.8 g (0.11 mol) of *S*-(+)-3-phenylbutyric acid in 450 mL of freshly distilled THF, add 15.3 mL (0.11 mol) of triethylamine under an atmosphere of argon.
2. Cool the mixture to –78°C, and add 14.2 mL (0.115 mol) of trimethylacetylchloride using a cannula. Stir the resulting white suspension for 10 min at –78°C, 1 h at 0°C, and recool to –78°C.



Scheme 5.

3. Meanwhile, in a different flask, prepare a solution of metallated D-oxazolidinone (**23,** Scheme 5) by the dropwise addition of 69 mL of *n*-butyllithium (1.6*M* in hexane) to a –78°C solution of 19.4 g of the D-auxiliary *(43)* in 450 mL of dry THF. Stir the mixture for 20 min at –78°C.
4. Transfer the lithiated chiral auxiliary via a cannula into the reaction flask containing the preformed mixed anhydride at –78°C. Stir the mixture at 0°C for 1 h and allow to warm to 23°C in 16 h.
5. Quench the mixture with 300 mL of saturated ammonium chloride solution. Evaporate THF *in vacuo*. Extract the product with (3 × 300 mL) of dichloromethane.
6. Wash the organic layer with 1*N* sodium hydroxide (2 × 100 mL) and 1*N* sodium bisulfate (1 × 100 mL), dry (anhd. magnesium sulfate), filter, and evaporate to give 30 g of colorless solid.
7. Purify by silica gel chromatography (elution with 15–30% ethyl acetate in hexane) to give 24.2 g (yield, 68%) of the desired compound *(34)* as a colorless solid, mp 82–84°. $[\alpha]^{23}D = -38.4°$ (c 0.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 1.35 (d, J = 6.8 Hz, 3H), 2.59 (dd, J = 14.8, 9.4 Hz,

Table 2
Diastereoselectivities of All Four Individual Isomers of β-Methylphenylalanine

Reactions	Diastereoselectivities of β-methylphenylalanine
L-auxiliary + (S)-(+)-phenylbutyric acid	(2R, 3R):(2S, 3S) = 95:5
L-auxiliary + (R)-(−)-phenylbutyric acid	(2R, 3R):(2S, 3S) = 99:1
D-auxiliary + (S)-(+)-phenylbutyric acid	(2R, 3R):(2S, 3S) = 99:1
D-auxiliary + (R)-(−)-phenylbutyric acid	(2R, 3R):(2S, 3S) = 95:5

1H), 3.1–3.2 (m, 2H), 3.3–3.5 (m, 2H), 4.1–4.2 (m, 2H), 4.61–4.67 (m, 1H), 7–7.3 (m, 10H).

3.3.2. General Procedure for Asymmetric Bromination of N*-Acyloxazolidinone and Subsequent Displacement by Azide: Illustrated by the Preparation of (4R)-3-(2'S,3'S)-2'-Azido-3'-(Phenylbutanoyl)-4-(Phenylmethyl)-2-Oxazolidinone,* **26**

1. Cool a solution of 26 g (0.08 mol) of *N*-acyloxazolidinone **24** in 180 mL of dichloromethane to –78°C.
2. Transfer a solution of 19.7 mL (0.112 mol) of freshly distilled diisopropylethylamine, followed by 111 mL of di-*n*-butylborontriflate (1*M* solution in DCM), via a cannula. Stir the mixture for 1 h at 0°C and then cool to –78°C.
3. Meanwhile in another flask, cool a suspension of 18.5 g of *N*-bromosuccinimide (0.10 mol) in 250 mL of dichloromethane to –78°C.
4. Transfer the boron enolate solution at –78°C via a cannula.
5. Stir the mixture at –78°C for 2 h.
6. Quench the mixture with 260 mL of aq. sodium bisulfate solution, and wash with 250 mL of water. Dry the organic layer (over sodium sulfate), filter, and evaporate to give the crude bromide as a brown oil that is used in the next step without purification.
7. From ^{1}H-NMR of this crude material, the ratio of major and minor isomers of the two diastereoisomeric bromides is found to be 94:6 (by integration of the two doublets corresponding to the diastereomeric bromides at δ 6.2).
8. Purify a small amount of this bromide (Scheme 5) by silica gel chromatography (elution with 90% hexane and 10% ethyl acetate). From the eluant, analytically pure bromide crystallizes on standing. The bromide has the following physical characteristics: mp 94–95°. $[\alpha]^{23}_D = -38°$ (c 0.5, $CHCl_3$).
9. Dissolve the crude bromide from the above reaction in 100 mL of acetonitrile, and add 51 g (0.32 mol, 5.5 Eq) of tetramethylguanidium azide

in one portion at 0°C. Warm the mixture to ambient temperature, and stir for 16 h.

10. Monitor the reaction (by ^{1}H-NMR) by the disappearance of signal (doublet) for the proton α to Br at δ 6.2 and appearance of signals for the proton α to the azide at δ 5.36.
11. Quench the reaction by the addition of 200 mL of saturated aq. sodium bicarbonate.
12. Extract the resulting mixture three times with dichloromethane (3 × 100 mL). Wash with water (3 × 100 mL), 6*N* HCl (1 × 100 mL), water (1 × 100 mL), 0.1*N* sodium bicarbonate (1 × 100 mL), and brine (1 × 100 mL).
13. Dry the organic extracts (anhd. sodium sulfate), filter, and evaporate *in vacuo*. Purify the resulting α-azido carboximide by silica gel chromatography (elution with 90% hexane and 10% ethylacetate) to give 17.9 g (84%) of azide **26** as a colorless solid. mp 84–86°. $[\alpha]^{23}D = +80.8°$ (c 1.1, $CHCl_3$). CIMS (isobutane), m/z (relative intensity) $M^+ + 1 = 365$ (2%), $M^+ + 1 - N_2 = 337$ (8%), $M^+ + 1 - N_3H = 322$ (15%); IR ($CHCl_3$): 2103, 1771, 1689 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 250 MHz): δ 1.32 (d, J = 7 Hz, 3H, β-CH_3); 2.58 (dd, J = 14.9, 9.4 Hz, 1H); 3.10–3.2 (m, 2H); 4.11 (m, 2H); 4.60 (m, 1H); 5.23 (d, J = 9.2 Hz, α-H, 1H); 7 1–7.3 (m, 10H).

3.3.3. General Procedure for the Removal of Chiral Auxiliary: Illustrated by the Preparation of (2S)-Azido-(3R)-Phenylbutanoic Acid, ***27***

1. Cool a solution of 12 g (0.032 mol) of acylazide **26** in 450 mL of THF and 175 mL of water to 0°C, and treat with 12.2 mL (0.13 mol) of 31% hydrogen peroxide, followed by 2.8 g of lithium hydroxide monohydrate (0.064 mol).
2. Stir the mixture for a total of 30 min.
3. At this time, thin-layer chromatography (hexane: ethyl acetate:acetic acid = 8:1.9:0.1) indicates complete disappearance of the starting material.
4. Quench the reaction with a solution of 0.5*N* sodium bicarbonate. Remove tetrahydrofuran *in vacuo*.
5. Extract with dichloromethane (5 × 100 mL) to give the recovered chiral auxiliary. Cool the aqueous layer to 0°C and acidify with 6*N* hydrochloric acid.
6. Extract with ethyl acetate (5 × 200 mL), dry (anhd. sodium sulfate), filter, and remove solvent to leave the azido acid as an oil.
7. Purify by silica gel chromatography (elution with 7:2.9:0.1 = hexane:ethyl acetate:acetic acid) to give 6 g (91%) of pure azido acid **27** as a light-yellow oil. $[\alpha]^{23}_D = -11°$ (c 1.0, $CHCl_3$). TLC, $R_f = 0.57$ (elution with 7:2.9:0.1 = hexane:ethyl acetate:acetic acid). CIMS (isobutane), m/z (rela-

tive intensity) $M^+ + 1 = 206$ (38%). ^{1}H-NMR ($CDCl_3$, 250 MHz): δ 1.37 (d, J = 7.2 Hz, 3H, β-CH_3); 4.06 (d, J = 7 Hz, 1H, α-H); 7.26–7.33 (m, 5H, aryl-H); 9.1 (s, 1H, —COOH). IR (film): 2600–3400 cm^{-1} (br, —OH); 2113 cm^{-1} (s, N_3); 1712 cm^{-1} (s, C=O).

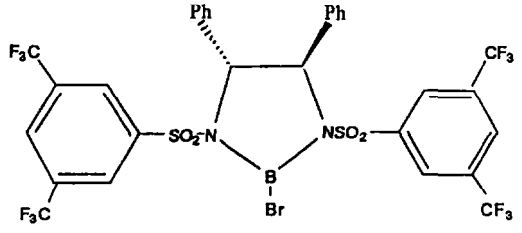
3.3.4. Threo-L-(2S, 3R)-β-Methylphenylalanine

1. To a solution of 2.7 g of azido acid **27** from the above reaction, in 110 mL of glacial acetic acid, add 30 mL of water in a Parr hydrogenation vessel.
2. Bubble a stream of argon through this solution for 5 min, and add 1 g of 10% Pd/C.
3. Hydrogenate the mixture at 30 psi for 24 h, then add 100 mL of water, and filter off the catalyst.
4. Add to the filtrate 20 mL of hydrochloric acid, and remove the solvents *in vacuo*.
5. Add 300 mL of anhd. ether to the residue. Filter the precipitated solid by suction filtration, and dry to give 2.2 g (80%) of the amino acid as its hydrochloride salt.
6. Purify a small amount of this amino acid by ion-exchange chromatography (*see* Chapter 2, *PAP*) (Amberlite, IR 120, H^+).
7. Elute with 10% ammonium hydroxide. The analytical data of the purified *threo*-L-(2S, 3R)-β-methylphenylalanine are listed below: mp 190–192°. $[\alpha]^{23}_D = -5.3°$ (c 0.75, H_2O), Lit (–5.8°, c 1.0, H_2O). CIMS (isobutane), m/z (relative intensity) $M^+ + 1 = 180$ (100%). ^{1}H-NMR (250 MHz, D_2O, dioxane as std at δ 3.55): δ 1.18, (d, J = 7.3 Hz, 3H, β-CH_3); 3.33 (m, 1H, β-H); 3.73 (d, J = 4.9 Hz, 1H, α-H); 7.15–7.25 (m, 5H, aryl hydrogens).
8. Thin layer chromatography of this compound on a chiral TLC plate shows only one enantiomer $R_f = 0.65$ (4:1:1 = acetonitrile:methanol:water). HPLC analysis of the *N*-acetyl derivative of this amino acid shows >99:1 ratio of *threo* to *erythro* isomers.

Recently, Font and associate reported an enantioselective synthesis of both (–)-*erythro*- and (–)-*threo*-γ-hydroxynorvaline *(44)*. They started with D-ribonolactone to prepare 5-deoxy-D-ribonolactone by the methods of Papageorgiou and Benezra *(45)*. The obtained 5-deoxy-D-ribonolactone was converted to a tosylate, which was readily displaced by azide. The azide subsequently underwent reduction, and ring opening of the lactone to afford (–)-erythro-γ-hydroxynorvaline; (–)-threo-γ-hydroxynorvaline was prepared using a similar process. Very recently, Font and associates synthesized (–)-4,5-dihydroxy-D-*threo*-L-norvaline using the same starting material *(46)*. The stereochemistry of the azide displacement is very unusual in that retention of configuration was

obtained. Similar processing of azide afforded the final γ,δ-dihydroxy-D-threo-L-norvaline. We would like to propose a mechanism for this unexpected retention of configuration. We think it may be the result of solvent involvement in the reaction. Since the authors did not mention the experimental details, we suppose that they did not isolate the triflate intermediate; pyridine is a good nucleophile, and since it is the solvent in the reaction, it may participate in the overall reaction to cause the double inversion of the configuration at the reaction center.

Frejd and associates reported a nice synthesis of γ-hydroxyisoleucine *(47)* using an asymmetric epoxide, benzyl 2,3-anhydro-4-*O*-(^{t}butyldimethylsilyl)-β-L-ribopyranoside, as starting material. They opened the epoxide ring by regioselective methylation using trimethyl aluminum. The hydroxy compound obtained was converted to another epoxide asymmetrically, and it in turn underwent amination by treatment with $Ti(O^iPr)_2(N_3)_2$ via an S_N2 mechanism. The azide obtained was oxidized to the α-azido acid, which was reduced to the final (2R,3R,4R)-γ-hydroxyisoleucine. The C-2 diastereomeric γ-hydroxyisoleucine also was prepared by a slightly different process in which the amination reagent they used was HN_3, DEAD, and Ph_3P. In this regard, it is worth mentioning that recently Fleming and Sharpless reported selective transformations of *threo*-2,3-dihydroxy esters *(48)*. This transformation can be used for the asymmetric synthesis of β-hydroxy α-amino acids starting from α,β-unsaturated esters following by oxidation to *threo*-2,3-dihydroxy esters. The obtained esters were transformed to α-hydroxy sulfonate esters with high regioselectivity (at C-2). These esters are ready for azide displacement to give α-azido-3-hydroxy esters, which are the precursors of β-hydroxy α-amino acids. Corey and Chai *(49)* also reported an asymmetric synthesis of β-hydroxy α-amino acids precursors using the reagent shown below:

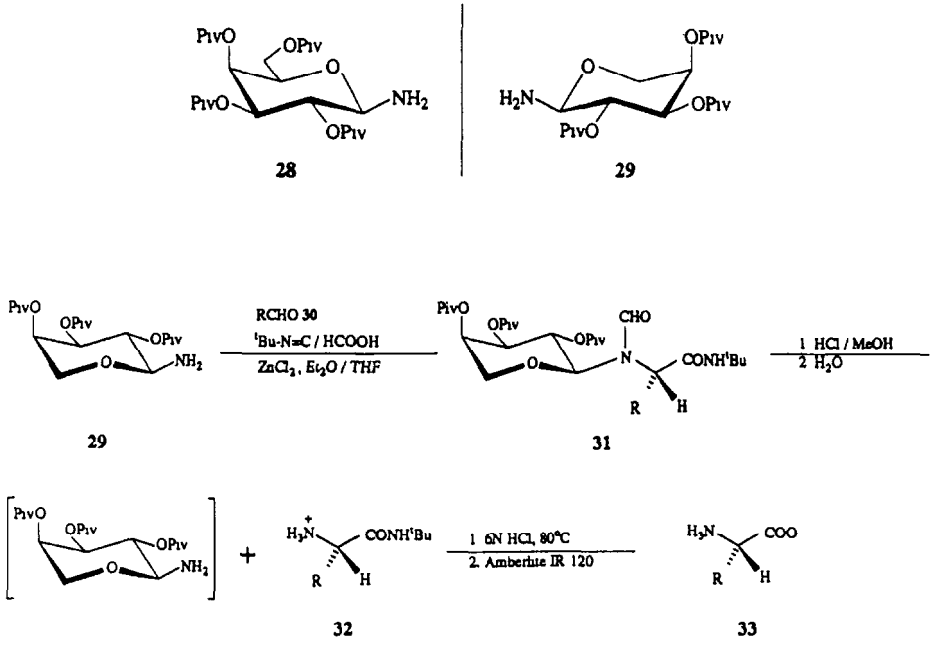


This compound induces a highly enantioselective aldol reaction between achiral aldehydes and ^{t}butylbromoacetate. The α-bromo-β-hydroxy

^{t}butyl esters obtained can undergo azide displacement and subsequent conversion to β-hydroxy α-amino acids.

3.4. Asymmetric Strecker Syntheses

The Strecker method is one of the traditional methods to prepare α-amino acids *(50)*. Although it is relatively convenient compared to most other methods, surprisingly, not much work has focused on this methodology. The basic idea for asymmetric synthesis via this method was the formation of a chiral Schiff base by condensation between an optically active amine and an aldehyde, or by condensation between an optically active aldehyde and an amine. Subsequent addition of HCN followed by hydrolysis should afford optically active α-amino acids. Harada and Okawara contributed based on the modifications of this methodology in the 1960s and 1970s *(51)*, and more recently, Kunz et al. have provided new insights *(52–54)*, including the use of carbohydrates as chiral templates. They found that the asymmetric induction was dependent on the solvent when using carbohydrate templates. For example, when using pivaloyl-D-galactosylamine **28** (Scheme 6) as a chiral template, (R)-diastereomeric amino nitriles were obtained in excess if the reactions were carried out in isopropanol in the presence of zinc chloride *(52)*, but (S)-diastereoisomeric amino nitriles were preferred if the reactions were carried out in chloroform. Based on these results, they used 2,3,4-tri-*O*-pivaloyl-2-D-arabinopyranosylamine **29** *(54)* (Scheme 6), which is a pseudo mirror-image of **28** as a chiral template (Scheme 6). **29** was condensed with aldehyde **30** in the presence of zinc chloride in THF to afford (α-D, 2S)-**31** with high selectivity (*see* Table 3). Treatment of (S)-**31** with hydrogen chloride in methanol followed by addition of water led to removal of the *N*-formyl group and the cleavage of the *N*-glycoside, which on acid hydrolysis gave the pure (S)-α-amino acid **33** (Table 4). Very recently, Kunz and associates reported another application of this methodology *(55)* starting with 2,3,4-tri-*O*-acetyl-α-arabinopyranosyl azide, a compound first prepared by Paulsen et al. *(56)*. This azide was then converted to the amine, the acetyl-protecting groups were changed to pivaloyl-protecting groups, and the chiral amine was condensed with aldehydes to give *N*-arabinosylimines, which were coverted to α-amino nitriles (L/D = 7–10:1). The nitriles were purified by recrystallization to obtain the pure L-amino nitriles (83–84% yield), which underwent acidic hydrolysis to provide L-phenylglycine and other L-amino acids. The



Scheme 6.

above chiral amine also can be converted to *N*-formyl-*N*-arabinosyl amino acid amides with better diastereoselectivity of (L/D = 20–30:1). These L-amino acid amides could be purified by either crystallization or flash chromatography in high yield (85–91%). The free enantiomerically pure L-amino acids were easily released from the carbohydrate templates by a two-step acidic hydrolysis. We provide here a specific example for the synthesis of L-2-(4-chlorophenyl)-α-amino acid **40** (Scheme 7).

3.4.1. α-D-Arabinopyranosyl Azide

1. Add 1*N* NaOMe in MeOH (1 mL) to a solution of 2,3,4-tri-*O*-acetyl-α-D-arabinopyranosyl azide **34** (0.1 mol) in MeOH (200 mL).
2. After 2 h, neutralize the solution using ion-exchange resin IR 200 (H^+ form 3 g), filter, and evaporate the solvent *in vacuo*. α-D-arabinopyranosyl azide: yield 100%; mp 93°; $[\alpha]^{22}_D = -21.2°$ (c = 1, H_2O). ^{13}C-NMR ($CDCl_3$/DMSO-d_6/TMS): δ = 67.66, 67.85, 70.20, 72.50 (C-2–C-5), 90.65 (C-1).

3.4.2. 2,3,4-Tri-O-Pivaloyl-Glycosyl Azide, 35

1. Add pivaloyl chloride (40 mL) dropwise to a solution of the α-D-arabinopyranosyl azide (0.1 mol) in pyridine (150 mL) at 0°C.

Table 3
Diastereoselective Ugi Synthesis
of *N*-Arabinopyranosyl Amino Acid Amides **31(a–e)**

Product	R	Reaction temp., °C/time, h	Kinetic ratio (C-2)S:(C-2)R	Yield% of pure (C-2)S-**31**
31a	$(CH_3)_3C$—	–25/72	97 3	85
31b	$PhCH_2$—	–78/24	97 3	87
31c	*p*-$ClC_6H_4CH_2$—	–25/24	98:2	91
31d	2-furyl	–25/24	96:4	85
31e	2-thienyl	–25/24	4:96	85 (C-2)R-**31**

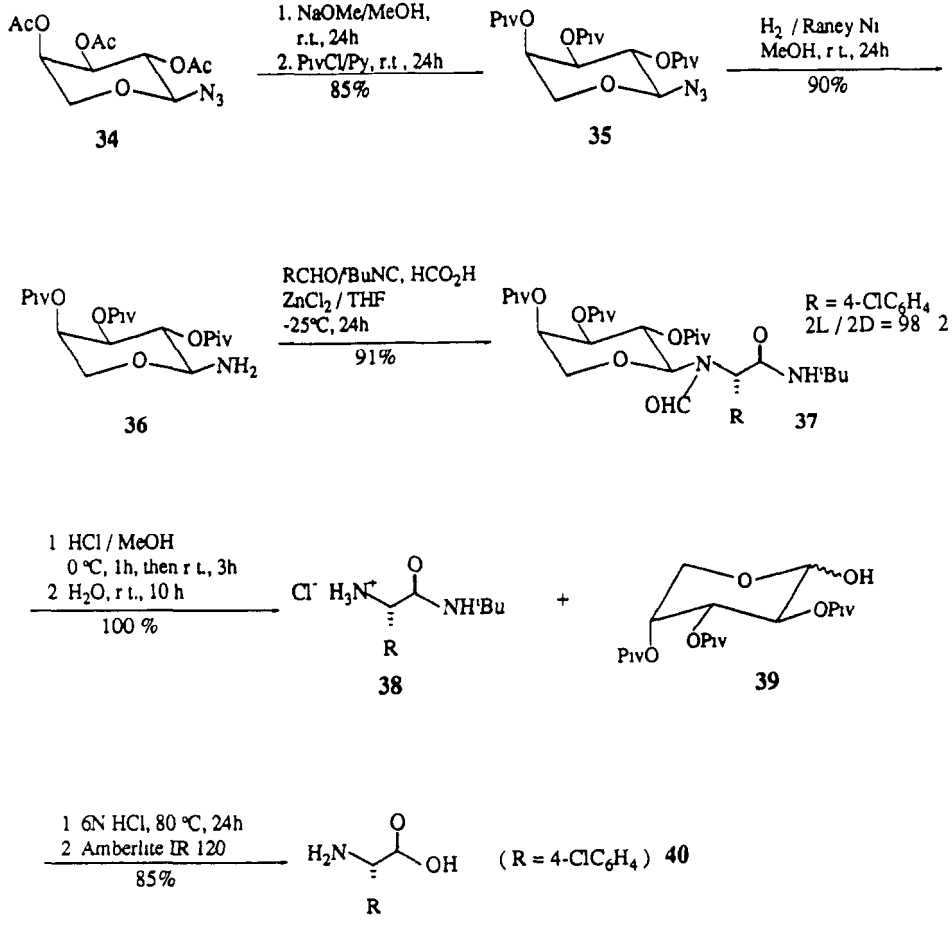
Table 4
(S)-Amino Acids **33** via Hydrolysis of
N-Arabinopyranosyl (S)-Amino Acid Amides **31(a–e)**

Product	R	Overall yield, %	$[\alpha]_D^{22}$
33a	$(CH_3)_3C$—	70	+8.5 (c 2, 1 5*N* HCl)
33b	$PhCH_2$—	82	–33.5 (c 0.5, H_2O)
33c	*p*-$ClC_6H_4CH_2$—	85	+139 5 (c 1, 1*N* HCl)

2. After 24 h at room temperature, evaporate pyridine and pivaloyl chloride *in vacuo*, dissolve the residue in $CHCl_2$ (200 mL), wash with 2*N* HCl (100 mL), sat. aq. $NaHCO_3$ (5 × 50 mL) and H_2O (100 mL), dry ($MgSO_4$), and concentrate *in vacuo*.
3. Recrystallize from MeOH to deliver pure compound: 2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl azide **35:** yield 89%; mp 90°; $[\alpha]^{22}_D$ = + 0.93° (c = 1, $CHCl_3$); $C_{20}H_{33}N_3O_7$ calc (%). C 56.19, H 7.78, N 9.83; found C 56.15, H 7.77, N 9.92. ^{1}H-NMR ($CDCl_3$/TMS): δ = 4.54 (d, 1H, $J_{1,2}$ = 9.7 Hz, 1-H), 5.08 (dd, 1H, $J_{3,4}$ = 3.3 Hz, 3-H), 5.19 (dd, 1-H, 2-H), 5.23 (m, 1H, 4-H).

3.4.3. Tri-O-Pivaloyl-Glycosylamine, ***36***

1. Hydrogenate a solution of the *O*-pivaloylated glycosyl azide **35** (0.1 mol) in MeOH (250 mL, containing 1–5% of CH_2Cl_2) under atmospheric pressure in the presence of Raney Ni (10 g).
2. After 3 h (TLC control), remove the catalyst by centrifugation, evaporate the solvent *in vacuo*, and recrystallize the remaining residue from MeOH. 2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosylamine **36**: yield 88%; mp 106°C; $[\alpha]^{22}_D$ = –46.7° (c = 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$/TMS): δ = 4.02 (d, 1H, $J_{1,2}$ = 8.4 Hz, 1-H), 5.07 (dd, 1H, $J_{3,2}$ = 10.2 Hz, $J_{3,4}$ = 3.3 Hz; 3-H), 5.01 (dd, 1H, 2-H), 5.18 (m, 1H, 4-H).



Scheme 7.

3.4.4. N-*Formyl*-N-*Glycosyl Amino Acid* N'-tert-*Butylamide*, **37**

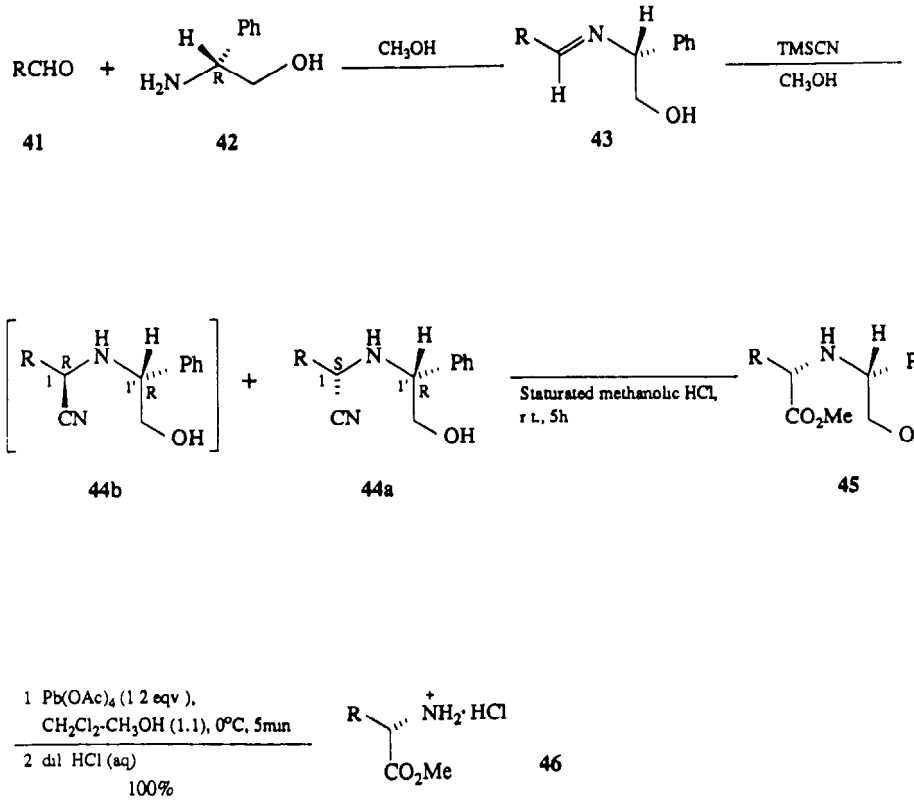
1. Add $ZnCl_2$ (4 mmol, as 2.2 molar solution of the ET_2O complex in CH_2Cl_2) to a solution of the glycosylamine **36** (4 mmol), the *p*-chloro-benzaldehyde (4.1 mmol), formic acid (4.4 mmol), and *t*-BuNC (4.2 mmol) in THF (30 mL), cooled to –25°C.
2. Monitor the reaction by TLC (light petroleum ether/ETOAc).
3. After complete disappearance of **36**, evaporate the solvent *in vacuo*, dissolve the residue in CH_2Cl_2 (50 mL) extracted with sat. aq. $NaHCO_3$ (2 × 100 mL) and with H_2O and dry ($MgSO_4$).
4. Evaporate the solvent *in vacuo*. The crude mixture of diastereomers obtained almost quantitatively (2L:2D = 98:2) is investigated by HPLC (on

120-5m C18 [reverse phase] in MeOH/20% H_2O). Recrystallize or purify by flash chromatography to deliver the pure *N*-formyl-*N*-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)-L-amino acid *N'-tert*-butylamides **37** in high yield. *N*-formyl-*N*-(2,3,4-tri-*O*-pivaloyl-α-D-arabinopyranosyl)-L-amino acid *N'-tert*-butylamides **37**: yield 91%; mp 202°C; $[\alpha]^{20}_D = -36.8°$ (c = 1, MeOH); $C_{33}H_{49}ClN_2O_9$ (653.2): satisfactory elemental analysis obtained, C m 0.1, H m 0.15, N m 0.1; ^{1}H-NMR ($CDCl_3$/TMS): δ = 5.17 (d, $J_{1,2}$ = 9.4–9.6 Hz, 1-H), 5.01 (s, a-CH).

3.4.5. Hydrolysis of **37** *to Give* L-*2-(4-Chlorophenyl)-2-Amino Acid,* **40**

1. Add a saturated solution of HCl in MeOH (3 mL) to the *N*-glycosyl-L-amino acid amide **37** (2 mmol) dissolved in dry MeOH (10 mL). Stir the mixture 1 h at 0°C and 3 h at room temperature. Add H_2O (2 mL), and stir the mixture for 10 h.
2. Evaporate the solvent, and dissolve the residue in H_2O (25 mL).
3. Extract the solution with pentane (2 × 20 mL). From the dried pentane solution, tri-*O*-pivaloyl-D-arabinopyranose **39** is recovered almost quantatively (>96%).
4. Evaporate the aqueous solution to dryness to give the amino amide **38** quantitatively.
5. Heat in 6*N* HCl at 80°C for 24 h.
6. Evaporate the solution to dryness, and distill off toluene (2 × 10 mL) from the residue. Then dissolve in water, and load on an ion-exchange column (Amberlite IR 120).
7. Wash the resin to neutral reaction of the eluent, and then elute the amino acid with aq. NH_4OH (3%).
8. Evaporate the ammonium salt solution *in vacuo* to give the L-amino acid **40** in crystalline form. Yield 85%; $[\alpha]^{20}_D = +139.5°$ (c = 1, 1N HCl). Data for the mp, elemental analysis, and NMR were not reported.

Chakraborty and associates synthesized optically pure L- and D-α-amino acids via diastereoselective Strecker synthesis *(57)* (Scheme 8) using α-phenylglycinol as chiral auxiliary. Imine **43** was generated from the condensation of respective aldehyde **41** and R-(–)-2-phenylglycinol **42**; **43** was then treated with trimethyl silyl cyanide to afford (1S, 1'R)-**44a** as the major product. The diastereoselectivities were good (*see* Table 5). After separation of the diastereoisomers **44a** and **44b**, the major isomer (1S, 1'R)-**44a** was converted to its *N*-substituted α-amino ester **45** by the treatment of saturated methanolic hydrochloric acid. Finally, the chiral auxiliary was easily removed from **45** by oxidative cleavage with



Scheme 8.

lead tetraacetate to give the amino acid **46**. Also recently, Cainelli and Panunzio synthesized a series of cyclic α-amino acids by a modified Strecker synthesis *(58)*.

3.5. Homologation of the β-Carbon

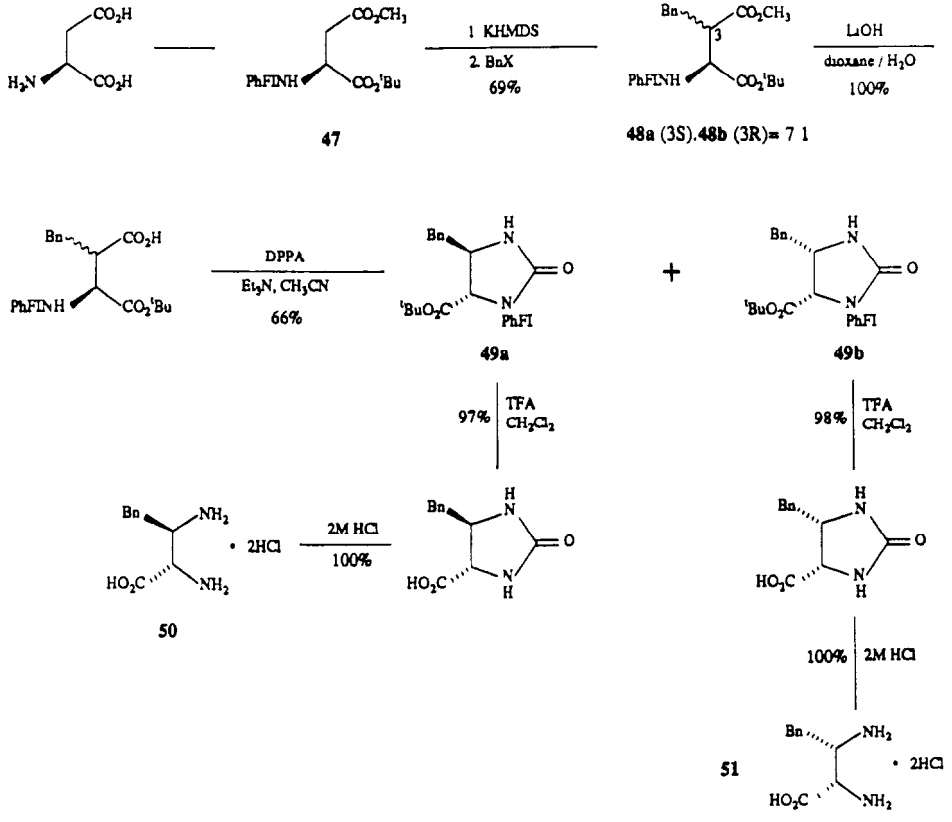
Homologation on the β-carbon of α-amino acids is a useful approach to many α-amino acids. L-Aspartic acid and proline derivatives are frequently used starting compounds in this approach, since their β or γ positions can be activated by electron-withdrawing groups. Since the strategy of this methodology is actually based on modifications of already available optically active α-amino acids, the idea is straightforward. Although the chemistry is usually not as sophisticated as seen in total syntheses of α-amino acids (amination methods, Stecker synthesis, and so forth), it is very attractive. Homologation of the γ-carbon also is cataloged in this

Table 5
Diastereoselective Strecker Synthesis
with R-(–)-2-Phenylglycinol **42** and Various Aldehydes

Entry	Aldehyde	Diastereoselectivity (1S,1'R)-**44a**:(1R,1'R)-**44b**	Total yield, %
1	Benzaldehyde (**41a**)	82:18	92
2	*p*-Tolualdehyde (**41b**)	85:15	90
3	*p*-Methoxybenzaldehyde (**41c**)	90.10	95
4	Isobutyraldehyde (**41d**)	84:16	95
5	Pivalaldehyde (**41e**)	88:12	92

section because it utilizes a similar strategy. Rapoport's group is one of the leading groups developing this methodology *(53)*, and recently they synthesized 2,3-diamino acids using this strategy (Scheme 9) *(60)* starting with aspartic acids. After protecting the carboxylic acid groups and amine group, the aspartic ester **47** was treated with KHMDS and BnX (X = Cl or Br) to provide adducts **48(a,b)** via electrophilic addition. Several aspartic acid derivatives were made with differences at the β-ester group. The diastereoselectivity of adduct **48(a,b)** can reach 25:1 (Fig. 1). Selective cleavage of the β-ester in **48(a,b)** followed by Curtius degradation using diphenylphosphorylazide (DPPA) yielded the cyclic 2,3-diamino derivatives **49(a,b)**. The *N*-protection was removed by treatment with THF, followed by acidic hydrolysis to afford the final β-substituted 2,3-diamino acids **50** and **51**.

Sasaki and associates reported a synthesis of β,γ-unsaturated α-amino acids *(61)*. They started with (2R)-2-$^{\alpha}$Boc-amino-3-phenylsulfonyl-1-(2-tetrahydropyranyloxy)propane or its (2S)-antipode. The C-1 hydroxy group and the protected amine group at C-2 position are the precursors of the acid group and amino group in the final amino acids, respectively. The β-homologation was achieved by electrophilic addition of aldehydes to the β-(C-3) position. The adducts underwent elimination of water and then oxidation to provide exclusively L-*Z*- or D-*Z*-propenylglycine. Baldwin et al. also have published extensively on "β-homologation" and have synthesized β,γ-unsaturated α-amino acids using this strategy *(62)*. They started with a diester of aspartic acid, α-^{t}Butyl-β-methyl-*N*-Z(S)-aspartate, which has an activated β-carbon. β-Homologation was achieved via electrophilic addition of ketones under basic conditions. Following elimination of water, decarboxylation, and hydrolysis, *E*- β,γ-



Scheme 9.

unsaturated α-amino acids (*E*:*Z* = 9:2) were obtained in good yields. In another recent paper, they reported a similar synthesis of β-alkylated aspartic acids using the same starting material, but different electrophiles (including alkyl halides) *(63)*. Parry and Lii also used the β-homologation strategy for the synthesis of *trans*-(+)-1-propenyl-L-cysteine sulfoxide *(64)*. The key step in this synthesis was the nucleophilic ring opening of 2-amino-β-propiolactone by an optically active thiol under basic condition. Finally, there are also some examples of γ-homologations. Baldwin and associates used dibenzyl *N*-trityl-(S)-glutamate as an γ-anion synthon to synthesize γ-carboxyglutamic acid and other γ-alkylated α-amino acids, via electrophilic substitution *(65)*. The electrophiles they used were carbonyl compounds, but diastereoselectivity was not high at the γ-posi-

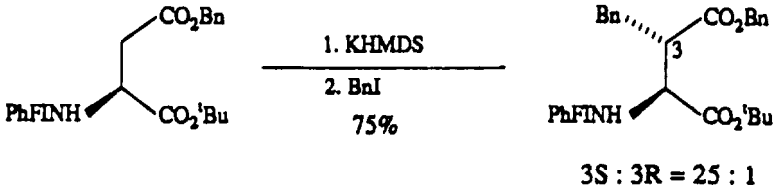
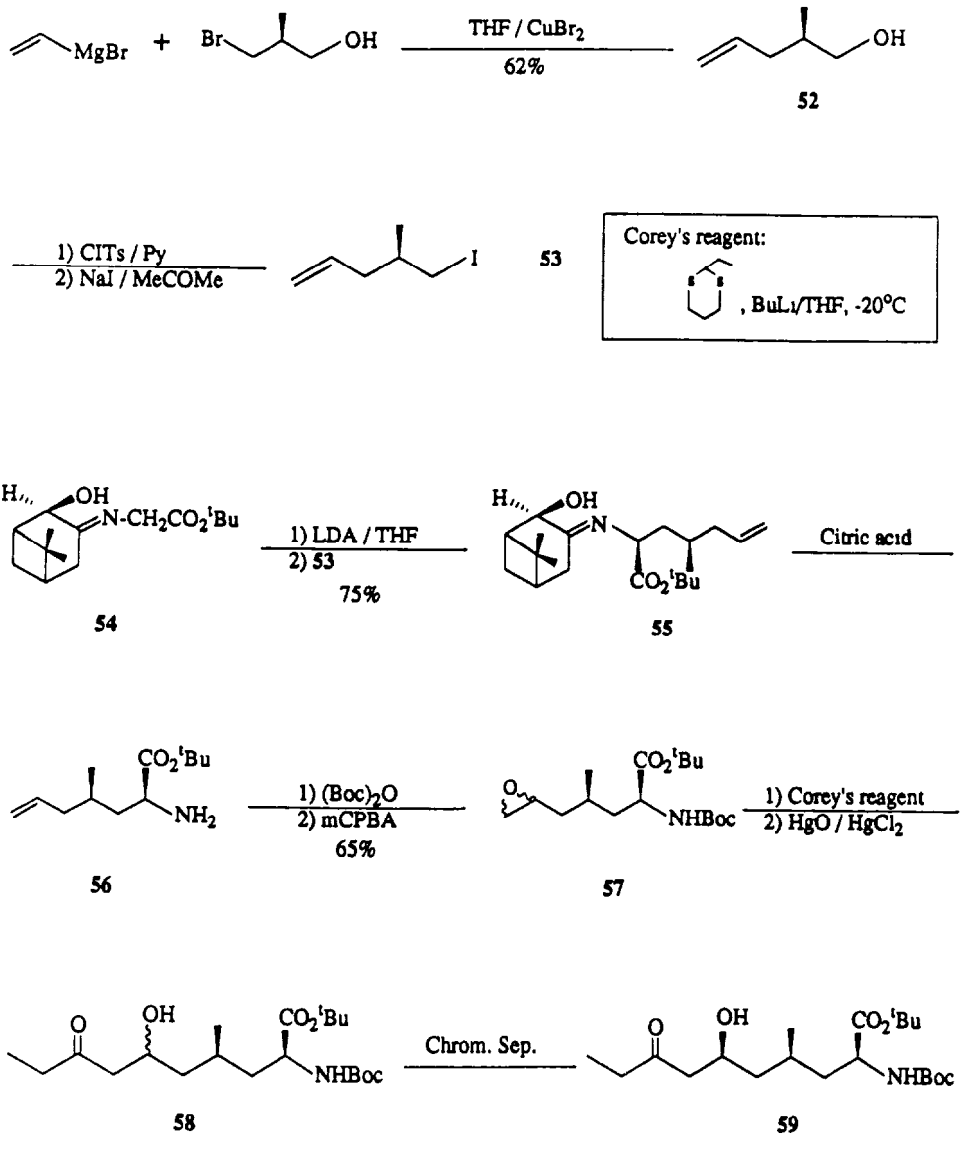


Fig. 1. Asymmetric alkylation at the b-carbon.

tion. Further work was done by the same group, in which they asymmetrically synthesized γ,δ-unsaturated α-amino acid by using the same synthon, α-^{t}Butyl γ-methyl *N*-trityl-(S)-glutamate. Baldwin and associates have tried to use (L)-pyroglutamic acid as a chiral starting material, to synthesize α-amino acids *(66)*. They first generated lactam enolate, followed by addition of electrophiles at the C-4 position in the ring system, although the diastereoselectivity is not high at the two new chiral centers (γ-C and δ-C). Elimination of water, ring opening, and deprotection provided the γ,δ-unsaturated α-amino acids. Hanson and asssociate used a six-membered ring γ,δ-unsaturated α-amino acid *(baikian)* as starting material to stereoselectively synthesized Δ^4-pipecolic acid *(67)*. Actually the γ-homologation product in this synthesis is not the goal, but only a key intermediate that can introduce an asymmetric alkylation on the ring system and recover the γ,δ-unsaturated functionality. This synthesis is an elegant application of γ-homologation. Hudlicky and Merola reported a synthesis of (–)-D-*erythro*- and (+)-L-*threo*-4-fluoroglutamic acid by the γ-isomerization of protected L-Hyp *(68)*. The stereocontrol step here is an oxidation by utilizing RuO_4 as oxidation reagent.

Very recently, El Hadrami and Lavergne synthesized (2S,4S,6S)-2-amino-6-hydroxy-4-methyl-8-oxodecanoic acid (AHMOD) *(69)*, a constituent of Leucinostatines that might be considered a pseudopeptide. They started with vinyl magnesium bromide and (R)-3-bromo-2-methyl propanol (Scheme 10) to obtain the vinyl alcohol **52**, which was converted to iodide **53**. Iodide **53** can alkylate the optically active Schiff base **54** under the basic condition through a Michael reaction. The chiral part of the Schiff base **54** works as a chiral auxiliary to achieve the diastereoselective alkylation. The adduct **55** underwent cleavage of the chiral auxiliary via acidic hydrolysis. The obtained terminal-vinyl-α-



Scheme 10.

amino ester **56** was oxidized, followed by protection of the amino group to afford epoxide **57**. The epoxide ring was opened by Corey's reagent (prepared from 2-ethyl-1,3-dithiane) via nucleophilic attack. The adduct underwent deprotection of the carbonyl function by the treatment of mer-

curic ions *(70)* to provide (6-*dl*)-AHMOD **58**. Final column chromatography separation afforded the (2S,4S,6S) diastereomer **59**.

3.6. Total Synthesis of α-Amino Acids

Urbach and Henning synthesized (1S,3S,5S)- and (1R,3S,5R)-azabicyclo-[3.3.0]octane-3-carboxylic acid from L-serine *(71)*. One five-membered ring product was directly obtained from the starting material, 3-bromocyclopentene. The other fused *N*-contained five-membered ring was achieved by an intramolecular radical cyclization of the appropriate optically active olefinic α-amino acid derivative. Unfortunately, the diastereoselectivity of the latter example was not as good as the former example; the former, with the ratio of (S,S,S) isomer to (R,S,R) isomer, is 1.25:1. Mulzer and associates did interesting work on the synthesis of the nonproteogenic amino acid (2S,2S,4S)-3-hydroxy-4-methylproline (HMP) and its enantiomer *(72)*. They started with the optically active tetrol derivatives that are readily available from D-mannitol. The key intermediates are optically active azido epoxides and their cyclic successor, diastereomerically pure 1-aza-bicyclo[3.1.0]hexanes, which underwent Staudinger aminocyclization to afford proline derivatives that could be converted to the final α-amino acids. The aminocyclization step was both stereo- and regiocontrolled. Hamada and coworkers synthesized γ-azetidinyl-β-hydroxy-α-amino acid as a precursor of mugineic acid *(73)*. The starting material they used was *O,O'*-isopropylidene-(R)-glyceric acid. There were two key steps in this total synthesis. One was the selective catalytic hydrogenation of a α,β-unsaturated five-membered lactone derivative; the other step was the catalytic hydrogenation of an aldehyde with the *p*-toluenesulfonate salt of benzyl (S)-2-azetidinecarboxylate by use of sodium cyanoborohydride to give the γ-azetidinyl-hydroxy-α-amino acid to mugneic acid in another earlier paper *(74)*. Schmidt's group accomplished quite a few total syntheses on complicated amino acids, which actually are cyclized small peptides *(75)*. Very recently, Schmidt and associate synthesized three different protected (2S,4R)-4-hydroxyornithines *(76)*. The key intermediates in this total synthesis are oxazolidine aldehyde, which is derived from (S)-malic acid in three steps, and a didehydroamino acid derivative that can undergo stereoselective catalytic hydrogenation to afford the final product: hydroxyornithine ester derivative. The catalyst for the hydrogenation was (R,R)-[Rh(1,5-COD)(DIPAMP)]$^{+}BF_4^{-}$; the obtained diastereoselectivity varies from 75:25 to 100:1.

Ⓟ — 10% cross-linking polyacrylic resin with a loading of 1 meg of aldehyde function per gram

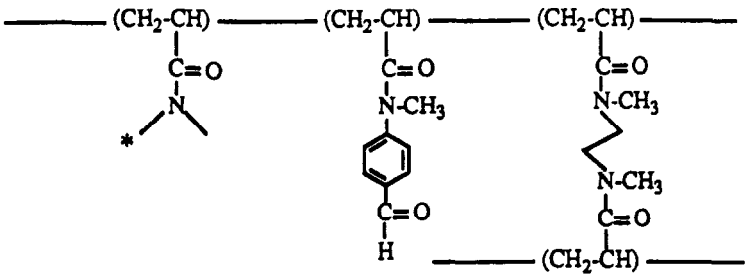
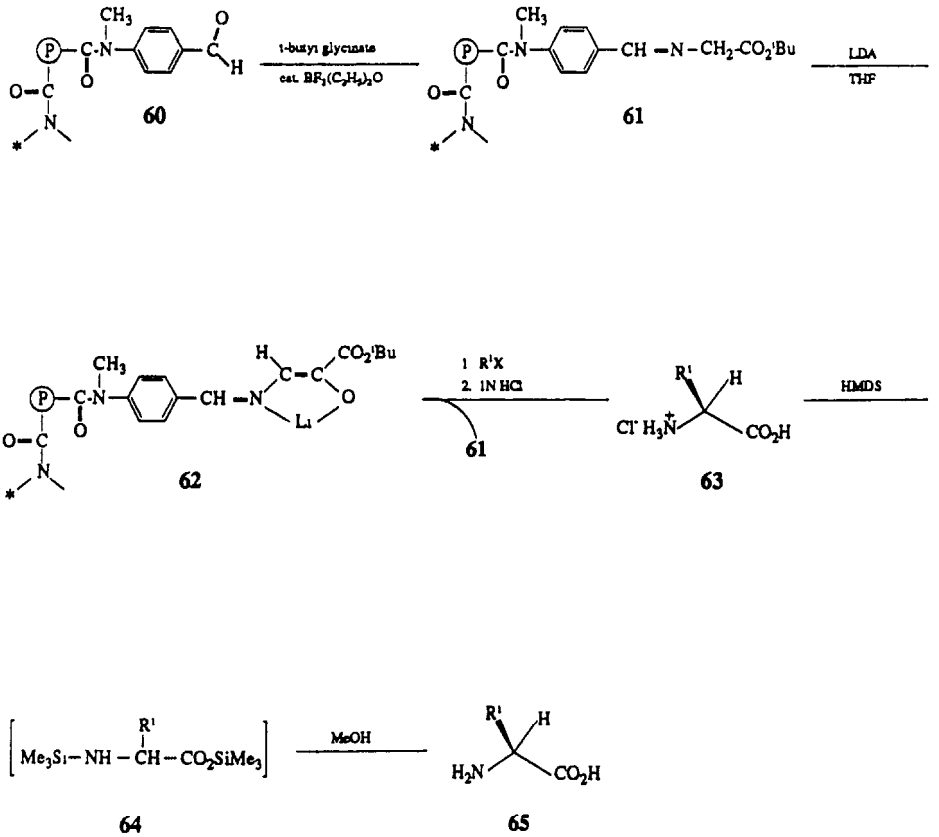


Fig. 2. Schematic structure of the polymer used in supermolecular asymmetric induction. (*indicates the location of chiral pedants).

3.7. Other Methods

α-Amino acids can be synthesized by many other different methodologies because these methodologies cannot be catalogued as a single separate class. Miscellaneous methods are very important not only because they involve many different kinds of chemistry, but also because of this recent exposure during the past few years *(77–93)*. We would like to introduce one interesting example in detail here. Daunis and coworkers synthesized α-amino acids via supramolecular asymmetric induction *(86)* Previously, similar ideas had been brought up by Saito and Harada *(81)*. The chiral inducer consists of crosslinked (10%) polyacrylic resin (with a loading of 1 mEq of aldehyde function/gram) and chiral pendant (Fig. 2). The chiral pendants they used were *N*-methyl α-phenylethylamine, prolinol, and prolinol methyl ester. Acid-catalyzed condensation of *t*-butyl glycinate with the above polymer **60** gave Schiff base **61** (Scheme 11). Compound **61** treated with LDA in THF afforded enolate **62**, which subsequently reacted with alkyl halide, followed by hydrolysis to give the crude amino acid hydrochloride **63**. In their paper, they estimated that there are about three to four chiral pendants surrounding the alkylation reaction center to give the chiral induction. Amino acid **63** was treated with hexamethyldisilazane to give the bistrimethylsilyl derivative **64**, which was then converted to pure α-amino acid **65** by the treatment of excess of methanol. Some of these results are shown in Table 6.



Scheme 11.

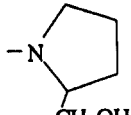
4. Use of α-Amino Acids

There are many potential uses for proteogenic α-amino acids, and here we will mention the two most common applications.

4.1. Utilization in Organic Synthesis

As already implied in the previous sections, there are many examples of using α-amino acids as starting materials as well as key intermediates in the asymmetric synthesis of other α-amino acids. We will give just a few such examples of employing α-amino acids in organic synthesis in this section. Easton and associates reported a regioselective formation of amidocarboxy-substituted free radicals *(94)*. The α-amino acids they used were *N*-benzolylvaline methyl ester and *N*-benzoylsarosine methyl ester. Rapoport et al. have used cysteine as a side chain to modify

Table 6
Diastereoselectivities of the Synthesis Using Prolinol as Chiral Pendant

Chiral pendant	Entry	Alkylating agent	Temp., °C	Yields, % **63**	**65** e e % (S)
	1	CH_3I	–78	75	88
	2	CH_3I	20	85	82
	3	i-C_3H_7I	–78	77	89
	4	i-C_3H_7I	20	84	84

Phycocyanobilin *(95)*. Jefford and associates synthesized (–)-Indolizidine 167B and (+)-Monomorine by using D-norvaline and L-alanine as starting materials *(96)*.

4.2. Utilization in Biological and Pharmacological Studies

The most important and widespread use of α-amino acids is in biological and pharmacological research. The biggest application in this area is the study of the chemistries, functions, and biological properties of peptides and proteins. As seen in the rest of this book, these studies have been so extensive that it is not possible to write a review about this application of α-amino acids in this short chapter. However, we want to give a few new examples here. Ueda and associates synthesized phenoxyacetyl-*N*-(hydroxydioxocyclobutenyl)cycloserine *(97)*. The L-isomer of this compound is thought to be a rational analog of lactivin, which, although not a β-lactam, has been shown to bind to penicillin-binding proteins, thus indicating a similar mode of action to the β-lactam antibiotics. In a recent report, Baldwin and associates gave further evidence for the involvement of a monocyclic β-lactam in the enzymatic conversion of β-L-α-amino-dipoyl-L-cysteinyl-D-valine into isopenicilin N *(98)*. Ouazzani and coworkers synthesized the enantiomeric α-amino phosphonic acids, phosphonic analogs of homoserine derivatives *(99)*. Such amino acids are believed to be the most important substitutes of the corresponding α-amino acids in the biological systems. Finally, in our laboratories *(100–103)*, we have successfully incorporated unusual α-amino acids (β-methyl phenylalanine, Tic, and D-Tic, and so on) for the conformational and topographical design of cyclic peptides in order to improve their biological profiles, and to obtain a more rational approach to conformation–activity relationships. The experimental results are optimistic.

5. Conclusion

In this discussion, we have reviewed several established methodologies for asymmetric synthesis of α-amino acids. In addition, there are many miscellaneous methods that are being developed, and some of them can provide pure optically active α-amino acids in high yields. We expect to see increased activity in the field.

Abbreviations

AcOH, acetic acid; AHMOD, 2-amino-6-hydroxy-4-methyl-8-oxodecanoic; AIBN, acidazo-(bis)-isobutyronitrile; BnX, benzyl halides (X = Cl, Br, I); Boc, *tert*-butyloxycarbonyl; $(Boc)_2O$, di-*tert*-butyldicarbonate; ^tBu, ^nBu (n-Bu), *tert*-butyl, butyl, respectively; Cbz, benzyloxycarbonyl; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; de, diastereomeric excess; DEAD, *N,N*-α-diethylazodicarboxylate; DPPA, diphenylphosphonylazide; e.e., enatiomeric excess; ET, ethyl; HMP, 3-hydroxy-4-methylproline; HMPA, hexamethylphosphoramide; L-Hyp, L-4-hydroxyproline; LDA, lithium diisopropylamide; MAA, methyl *N*-acetamidoarylate; MeBmt, (4R)-4-[(E)-2-butenyl]-4, N-dimethyl-L-threonine; *m*CPBA, *meta*-chloroperoxybenzoic acid; Me, methyl; MIC, minimum inhibitorial concentration; (2S, 4S)-MOD-BPPM, *see* Scheme 2; Ph, phenyl; PIV, pivaloyl; ^iPr,Pr, *iso*-propyl, propyl, respectively; [Rh-(1,5-COD)(DIPAMP)]$^+BF^-$, rhodium-(1,5-cyclooctadiene)-{1,2-ethanediylbis-[(o-methoxyphenyl)phosphine]}; TFA, trifluoro acetic acid; TfO (OTf), triflate; THF, tetrahydrofuran; Tic (or D-Tic), 1,2,3,4-tetrahydroisoquinoline-carboxylic acid.

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