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Asymmetric Synthesis Of Unusual Amino Acids: An Efficient Synthesis of Optically Pure Isomers of β-Methylphenylalanine.

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Abstract. Substitution of the diastereotopic β-hydrogens of many α-amino acids provides an approach to the three dimensional topographic control of peptide structure. Asymmetric synthesis of the desired amino acids is needed to facilitate these studies. All four individual isomers of β-methylphenylalanine, (2S,3S)-, (2R,3R)-, (2S,3R)- and (2R,3S)-β-methylphenylalanine have been synthesized in high optical purity. The stereochemistry at the β-center was set by the choice of starting material, either (+)- or (-)-3-phenylbutyric acid. These acids were attached to the appropriate D- or L-auxiliary (a 4-phenylmethyl-2-oxazolidinone) to give a 3′-phenylbutanoyl-4-phenylmethyl-2-oxazolidinone. Asymmetric bromination was accomplished via the chiral imide enolate bromination methodology of Evans and co-workers (*J. Am. Chem. Soc.* **1990**, *112*, 4011-40). Evidence for asymmetric induction was obtained from the X-ray structure of one of the intermediate bromides. The bromide was converted to the diastereoisomeric azide by S_N2 displacement using tetramethylguanidinium azide. After recovery of the chiral auxiliary by catalyzed hydrolysis, the chiral amino acid was obtained by catalytic hydrogenation over 10% Pd/C. All four isomers were obtained in enantiomeric purities of 95:5 to 99:1.

INTRODUCTION

A central goal in peptide and protein research is the development of rational approaches to the design of peptide and protein ligands with specific physical, chemical and biological properties[1]. A primary approach to the design of peptide ligands has involved the use of conformational constraints, which has provided an important rationale for peptide ligand development. A more recent complementary approach has utilized topographical design (by topography, we mean the "relative, cooperative three dimensional arrangement of the side chain groups in a polypeptide"[2]) of peptide ligands.[2-5] There is emerging evidence[2,6,7] to suggest that in some peptides, the backbone can act primarily as a scaffolding agent (template), and the side chain

Dedicated to Professor Gabor Fodor on the occasion of his 75 Birthday

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†Undergraduate research participants, part of this work was done as an Undergraduate Honor's Thesis (KVH).

groups then act as the primary locus for interaction with the receptor. In either case, structural features that could influence the side chain rotamer populations would modulate the peptide topography, and as a direct consequence, could significantly modulate their biological properties as well. From this perspective, the χ_1 (and other) side chain torsional angles are critical, and any structural feature that can bias or fix these angles to either gauche(-), trans, or gauche(+) conformations (Figure 1) would be useful. For example, based on simple steric considerations, replacing the pro S - β hydrogens in phenylalanine by a methyl group to give (2S, 3S) β-methylphenylalanine (Figure 2) makes the gauche(-) conformation significantly more stable than the trans or gauche(+) conformations. This is because there are two unfavorable steric interactions in the case of gauche(-) conformation whereas there are three unfavorable steric interactions in the case of gauche(+) or trans conformations. A similar argument for the case of the (2S, 3R) isomer suggests that the trans isomer will be expected to be more stable than the gauche(-) or gauche(+) conformations (Figure 2). Ready access to these amino acids is a enantiomerically pure form is needed to systematically pursue this research.

RESULTS AND DISCUSSION

In a preliminary account,[8] we have reported on an approach for the asymmetric synthesis of all the four isomers of β-methylphenylalanine. For reasons discussed above, the effects of these amino acids will be different for different peptides, and also for a given peptide, depending on the specific biological question to be addressed (e.g. the issues of selectivity and potency), particularly when dealing with multiple receptors.[5] Of the four possible isomers of β-methylphenylalanine, it is difficult to select 'a priori' the desired stereoisomer for a given peptide at a given receptor or other acceptor molecule, and in any case, further insight is needed into the compatibility of such structural modifications with peptide and protein secondary structures. Therefore, it is essential to have a practical synthesis of all the four isomers in high optical purity. In this paper we provide experimental details for a large scale synthesis of these amino acids.[9] In addition, we provide evidence for asymmetric induction from an X-ray structure analysis[10] of an intermediate bromide.

The general methodology for the asymmetric synthesis of these amino acids is illustrated by the synthesis of (2S, 3R)-β-methylphenylalanine (Scheme 1). Commercially available racemic 3-phenylbutyric acid was resolved[11] into its optical isomers via fractional crystallization of diastereomeric salts formed with S(-)-methylbenzylamine. From the partially enriched mother liquor, the R(-) isomer was obtained by fractional crystallization of diastereomeric salts formed with R-(+)-methylbenzylamine. The S-(+)-3-phenylbutyric acid thus obtained was converted[12] into a mixed anhydride with pivalic acid and was attached to the chiral auxiliary derived from D-phenylalanine. (The chiral auxiliary was obtained by reduction of D-phenylalanine with either borane-dimethylsulfide[13] or alternatively with lithium borohydride in the presence of chlorotrimethylsilane[14]).

The N-acyl oxazolidinone **3c** was converted to a boron enolate by use of dibutylborontriflate[15] in dichloromethane (Scheme 1). Stereoselective bromination was accomplished using NBS, and S_N2

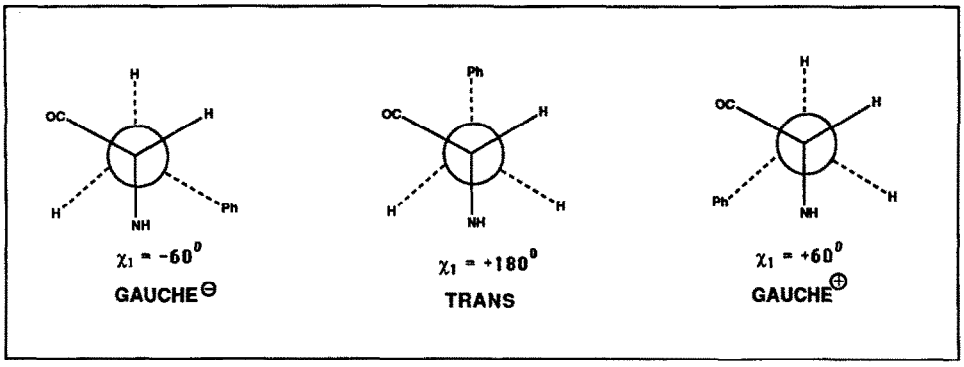


FIGURE-1

displacement of the resulting crude bromide by tetramethylguanidinum azide gave the diastereoisomeric azide 5c with high diastereoselectivity. To establish that the asymmetric induction had occurred as desired, the above bromide was purified by silica gel chromatography and recrystallized from ethyl acetate and hexane to give long needles which were submitted for X-ray analysis.[10] The compound had the predicted stereochemistry at all the three chiral centers.

A word of caution about the displacement reaction by organic azides. We have utilized dichloromethane as solvent and tetramethylguanidinium azide[16a] or tetrabutylammonium azide[16b] as the source of nucleophilic azide anion for these reactions. However, on one occasion, when using tetrabutylammonium

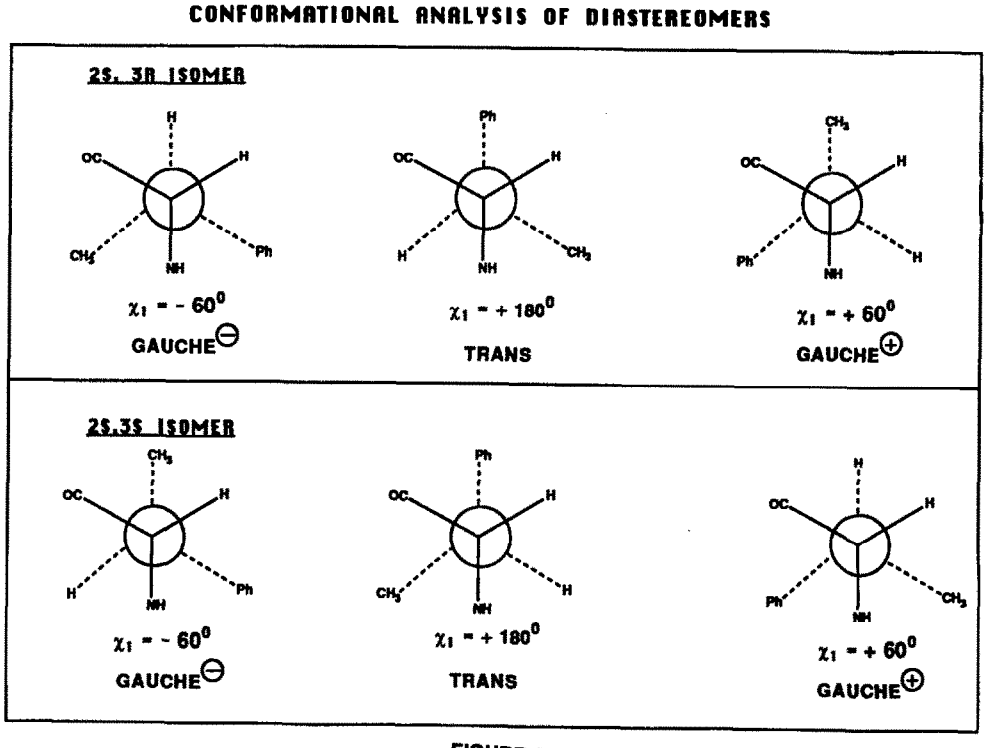
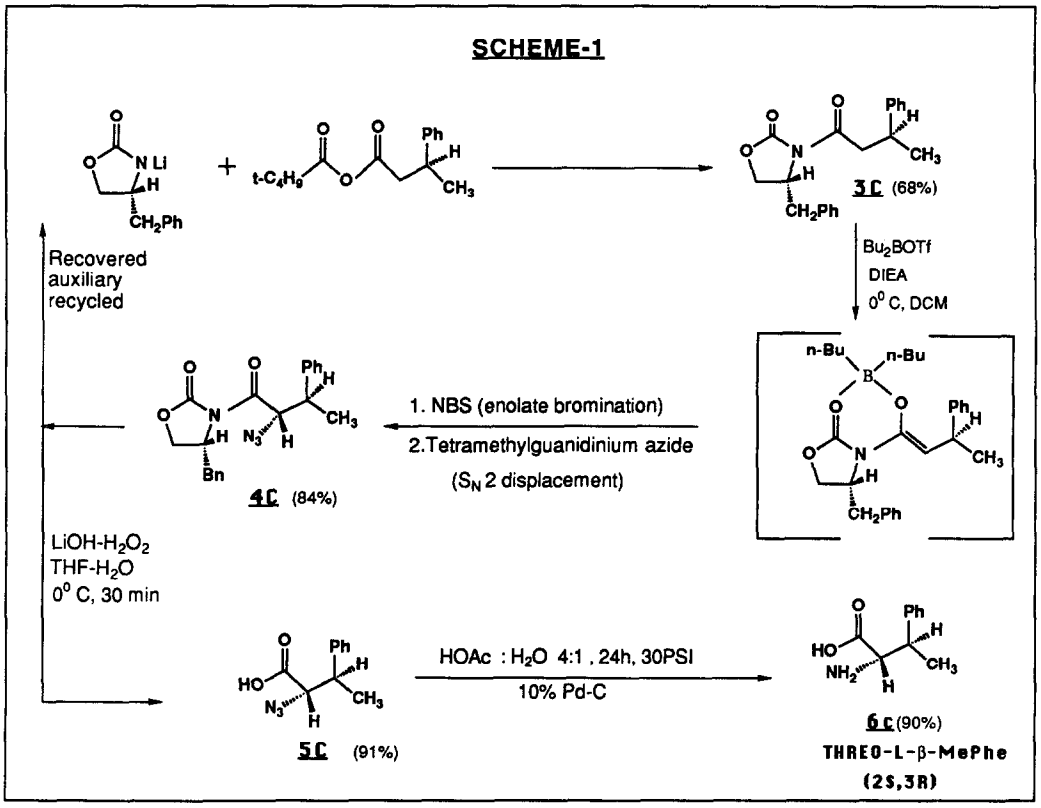


FIGURE-2



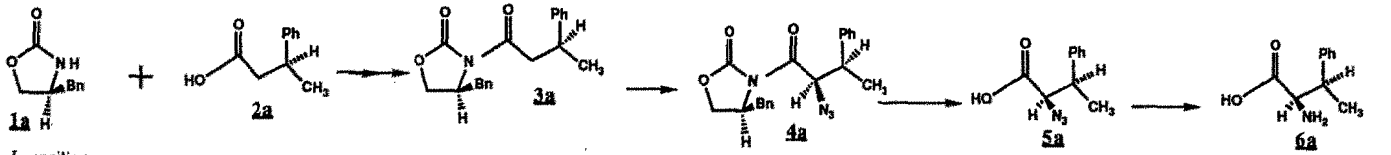
azide, a major explosion occurred when the solvent was being removed on a rotary evaporator. We traced the probable source of the explosion to an explosive by-product, bis-azidomethane, formed by reaction of dichloromethane with the nucleophilic azide.[17] We subsequently found that this problem can be avoided by using acetonitrile as a solvent. Preliminary experiments have indicated that this transformation also can be effected safely by carrying out the reaction using a polymeric azide[17,18] and filtering the polymer after the reaction was completed. No racemization was observed in any of these protocols.

Removal of the chiral auxiliary was effected by hydrolysis using LiOH in presence of hydrogen peroxide. Reduction (10% Pd/C, 1:1 AcOH: H_2O) of the resulting azido acid **5c**, Scheme 2) gave threo-L-β-methylphenylalanine. The diastereomeric purity of the resulting amino acids was determined by HPLC analysis[19] of the derived N-acetyl derivative [20b] with a mixture of threo and erythro-N-acetyl-β-methylphenylalanine prepared by the method of Kataoka et al.[21] serving as a standard.

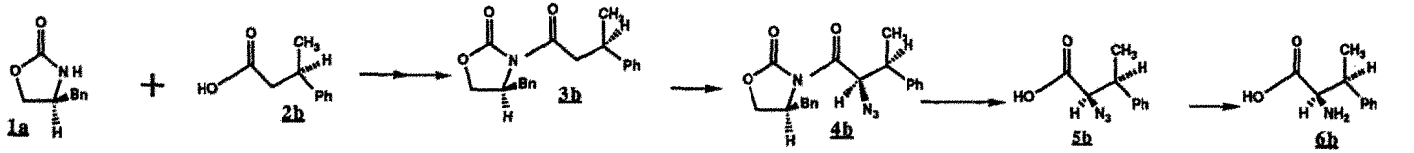
Utilizing the L-chiral auxiliary and R-(-)-3-phenylbutyricacid gave (2R,3S)-β-methylphenylalanine. The other two isomers were synthesized from the chiral auxiliary derived from D-phenylalanine and S-(+)- or R(-)3-phenylbutyric acid (Scheme 2). Since the stereochemistry at the β-carbon is set by the choice of optically pure starting materials (i.e., (+) or (-)-3-phenylbutyric acid) in this methodology, it is highly

SCHEME-2

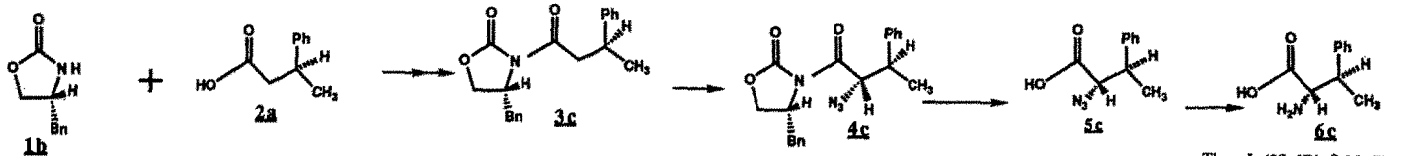
ALL THE FOUR INDIVIDUAL ISOMERS OF β- METHYLPHENYLALANINE HAVE BEEN SYNTHESIZED BY STARTING WITH A D OR L AUXILIARY AND (+) OR (-) 3-PHENYLBUTYRICACID.



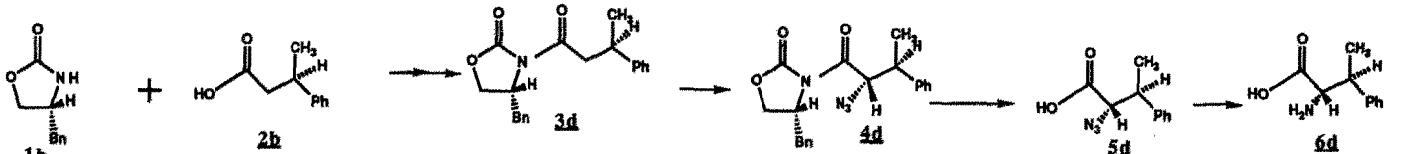
L- auxiliary — S-(+)-3-Phenylbutyric acid — Erythro-D-(2R, 3R) -β-Me Phe



L-auxiliary — R-(-)-3-Phenylbutyric acid — Threo-D-(2R, 3S) -β-Me Phe



D- auxiliary — S-(+)-3-Phenylbutyric acid — Threo-L-(2S, 3R) -β-Me Phe



D- auxiliary — R-(-)-3-Phenylbutyric acid — Erythro-L-(2S, 3S) -β-Me Phe

unlikely that enantiomeric impurities will be obtained in these syntheses. However, since the stereochemistry at the α-carbon is determined by the chiral auxiliary, it is possible to have (depending on the degree of asymmetric induction) minor amounts of diastereomeric impurities in the synthesized amino acids. Since the ^{1}H NMR spectra of erythro and threo isomers are distinctly different, minor impurities of undesired isomers were easily detected. All of the four isomers have been obtained in >95 % optical purities. The optical purities obtained for each asymmetric synthesis are given in Table I.

Table I. All of the Four Individual Isomers of β-Methylphenylalanine Have Been Synthesized in High Optical Purities.

		β-Methylphenylalanine
L-auxiliary + S-(+)-3-phenylbutyric acid	→ → →	(2R,3R):(2S,3S) 95:5
L-auxiliary + R-(-)-3-phenylbutyric acid	→ → →	(2R,3S):(2S,3S) 99:1
D-auxiliary + S-(+)-3-phenylbutyric acid	→ → →	(2S,3R):(2R,3R) 99:1
D-auxiliary + R-(-)-3-phenylbutyric acid	→ → →	(2S,3S): (2R,3S) 99:1

CONCLUSIONS

We have extended the method of Evans and co-workers[9a] for the asymmetric synthesis of the four stereoisomers of β-methylphenylalanine. The methodology meets the criteria of "research economics"[9a] in that it provides these unusual amino acids on large scales and in high optical purities. These amino acids, when incorporated into peptides, can modulate their topography, and as a direct consequence their biology. We have incorporated these amino acids into various peptide hormones and neurotransmitters including [D-Pen^2,D-Pen^5]enkephalin (DPDPE),[5] oxytocin, cholecystokinin-8 (CCK-8), α-melanotropin (α-MSH), the deltophins, glucagon, and somatostatin analogues. The synthesis and interesting biological results from these studies will be reported elsewhere.

EXPERIMENTAL SECTION

General. All reactions were performed under a dry argon atmosphere. Tetrahydrofuran was distilled from sodium/benzophenone ketyl prior to use. Dichloromethane, diisopropylamine and triethylamine were distilled from CaH_2. n-Butyllithium (1.6 M in hexane), N-Bromosuccinimide, dibutylborontriflate (1M solution in dichloromethane) were purchased from Aldrich Chemical Co. N-bromosuccinimide was recrystallized from water and dried *in vacuum* for 24 hr. Tetramethylguanidinium azide was prepared as described in the literature[16]. Column chromatography was performed on silica gel (70-230 mesh, 60Å). Analytical thin-layer chromatography was performed on E. Merck silica gel 60F-254 precoated plates and the spots were visualized with a UV light. Elemental analysis was performed by Desert Analytics, Tucson, Az. Melting points (uncorrected) were measured on Thomas Hoover capillary melting point apparatus. The term *in vacuo* refers to solvent removal via a Büchi rotary evaporator at water aspirator pressure followed

by evaporation at 0.5 mm for several hours. The S and R oxazolidinone chiral auxiliaries **1a** and **1b** (Scheme 5) were prepared according to previously reported methods.[22]

General Procedure for the Preparation of N-acyloxazolidinone: Illustrated by the Preparation of (4R)-3-(3'R)-3'-(phenylbutanoyl)-4-(phenylmethyl)-2-oxazolidinone, 3d.

To a stirred solution of 19.8 g (0.11 moles) of R-(-)-3-phenylbutyric acid[11] in 450 mL of freshly distilled THF, was added 15.3 mL (0.11moles) of triethylamine under an atmosphere of argon. The mixture was cooled to -78°C and 14.2 mL (0.115 moles) of trimethylacetylchloride were added using a cannula. The resulting white suspension was stirred for 10 min at -78°C, 1 hr at 0°C, and was re-cooled to -78°C.

Meanwhile, in a different flask, a solution of metallated R-oxazolidinone (**1b**, Scheme 5) was prepared 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 (see below) in 450 mL of dry THF. The mixture was stirred for 20 min at -78°C. The lithiated chiral auxiliary was transferred via a cannula into the reaction flask containing the preformed mixed anhydride at -78°C. The mixture was stirred at 0°C for 1 hr and was allowed to warm to 23°C in 16 hr. The mixture was then quenched with 300 mL of saturated ammonium chloride solution. THF was evaporated *in vacuo*. The product was extracted with (3 x 300 mL)of dichloromethane. The organic layer was washed with 1N sodium hydroxide (2 x 100 mL), 1N sodium bisulfate (1 x 100 mL), dried (anhd. magnesium sulfate), filtered and evaporated to give 30 g of colorless solid. Purification by silica gel chromatography (elution with 15-30% ethyl acetate in hexane) gave 26.4 g (74%) of the desired compound as a colorless solid, mp 110-112°C. $[\alpha]^{23}_D$ = - 65° (c 1.0, $CHCl_3$). 1H NMR ($CDCl_3$, 250 MHz) δ 1.4 (d, J=6.7 Hz, 3H), 2.6-2.8 (m, 1H), 3.1-3.3 (m, 2H), 3.3-3.5 (m, 2H), 3.9-4.2 (m, 2H), 4.4-4.6 (m, 1H), 7.22-7.39 (m, 10H). CIMS (Isobutane), m/e (relative intensity) 324 (M^+ + H, 100). Anal. Calcd for $C_{21}H_{21}NO_3$ (323.37): C, 74.28; H, 6.55; N, 4.30. Found: C,73.92; H, 6.63; N, 4.45.

Preparation of (4S)-3-(3'S)-3'-(phenylbutanoyl)-4-(phenylmethyl)-2-oxazolidinone, 3a. Following the general procedure described above, a solution of lithiated chiral auxiliary in 700 mL of THF was prepared from 30 g (0.17 moles) of L-auxiliary **1a** and 107 mL (0.17 moles) of n-butyl lithium (1.6 M in hexane), and was added to a 700 mL THF solution of mixed anhydride prepared from 30.6 g S-(+)-3-phenylbutyric acid[11] (0.17 moles), 23.7 mL (0.17 moles) of triethylamine and 22 mL of (0.18 moles) trimethylacetyl chloride. Following work-up and purification according to the general procedure described above, there was obtained 41 g (75%) of the product **3a** as a colorless solid. mp 110-112°C. $[\alpha]^{23}_D$ = + 68° (c 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz) d 1.4 (d, J=6.7 Hz, 3H), 2.6-2.8 (m, 1H), 3.1-3.3 (m,2H), 3.3-3.5 (m, 2H), 3.9-4.2 (m, 2H), 4.4-4.6 (m, 1H), 7.22-7.39 (m,10H). CIMS (Isobutane), m/e (relative intensity) 324 (M^+ + H, 100). Anal. Calcd for $C_{21}H_{21}NO_3$ (323.37): C, 74.28; H, 6.55; N,4.33. Found: C, 73.87; H, 6.63; N, 4.67.

Preparation of (4R)-3-(3'S)-3'-(phenylbutanoyl)-4-(phenylmethyl)-2-oxazolidinone, 3c. Following the general procedure described above, a solution of lithiated chiral auxiliary in 450 mL of THF was prepared from 19.4 g (0.11 moles) of the D- auxiliary and 69 mL (0.11 moles) of n-butyl lithium (1.6 M in hexane)

and was added to a 450 mL solution of mixed anhydride prepared from 19.8 g S-(+)-3-phenylbutyric acid[11] (0.11 moles), 15.3 mL (0.11 moles) of triethylamine and 14.2 mL of (0.11 moles) trimethylacetylchloride. Following work-up and purification as above, 24.2 g (68%) of a colorless solid **3c** was obtained. mp 82-84°C. $[\alpha]^{23}_D$ = - 38.4° (c 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz) δ 1.35 (d, J=6.8 Hz, 3H),2.59(dd, J=14.8, 9.4Hz, 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). CIMS (Isobutane), m/z (relative intensity) $M^+ + 1$ = 324 (15 %). Anal. Calcd for $C_{21}H_{21}NO_3$ (323.37): C, 74.28; H, 6.55: N, 4.33. Found: C ,74.26; H, 6.48; N, 4.45.

Preparation of (4S)-3-(3'R)-3'-(phenylbutanoyl)-4-(phenylmethyl)-2-oxazolidinone, 3b. Following the general procedure described above, a solution of lithiated chiral auxiliary in 700 mL of THF was prepared from 30 g (0.17 moles) of L- auxiliary and 107 mL of n-butyl lithium (1.6 M in hexane) and was added to a 700 mL solution of mixed anhydride prepared from 30.6 g S-(+)-3-phenylbutyric acid[11] (0.17 moles), 23.7 mL (0.17 moles) of triethylamine and 22 mL (0.18 moles) of trimethylacetyl chloride. Following work-up and purification according to the general procedure given above, there was obtained 37 g (68%) of colorless solid **3b**. mp 100-104°C. $[\alpha]^{23}_D$ = + 41° (c0.25, $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz) δ 1.35 (d, J=6.8 Hz, 3H), 2.59 (dd, J= 14.8, 9.4 Hz,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), 7.0-7.3 (m,10H). CIMS (Isobutane), m/z (relative intensity) $M^+ + 1$ = 324 (32 %). Anal. Calcd for $C_{21}H_{21}NO_3$ (323.37): C, 74.28; H, 6.55, N, 4.33. Found: C, 73.98; H, 6.50; N, 4.42.

General Procedure for Asymmetric Bromination of N-Acyloxazolidinones and Subsequent Displacement by Azide; Illustrated by the Preparation of (4R)-3-(2'S, 3'S)-2'-Azido-3'-phenylbutanoyl)-4-(phenylmethyl)-2-oxazolidinone, 4d. A solution of 26 g (0.08 moles) of N-acyloxazolidinone **3d** in 180 mL of dichloromethane was cooled to -78°C. A solution of 19.7 mL (0.112 moles) of freshly distilled diisopropylethylamine, followed by 111 mL of di-n-butylborontriflate (1M solution in DCM), was transferred via a cannula. The mixture was stirred for 1 hr at 0°C and then cooled to -78°C.

Meanwhile in another flask, a suspension of 18.5 g of N-bromosuccinimide (0.10 moles) in 250 mL of dichloromethane was cooled to -78°C. The boron enolate solution at -78°C was transferred via a cannula. The mixture was stirred at -78°C for 2 hr. It was then quenched with 260 mL of aq sodium bisulfate solution, washed with 250 mL of 1N sodium thiosulfate and 250 mL of water. The organic layer was dried (over sodium sulfate), filtered and evaporated to give the crude bromide as a brown oil, which was used in the next step without purification. From the ^1H NMR of this crude material, the ratio of major and minor isomers of the two diastereomeric bromides was found to be 94:6 (by integration of the two doublets corresponding to the diastereomeric bromides at δ 6.2).

The crude bromide from the above reaction was dissolved in 150 mL of dichloromethane (or acetonitrile). Tetramethylguanidinium azide[16a] (68 g, 0.43 moles, 5.4 eq) was added in one portion at 0°C. The mixture was warmed to and stirred at ambient temperature for 16 hr. The reaction can be monitored conveniently (by ^1H NMR) by the disappearance of signal (doublet) for the proton δ to Br at δ 6.2 and

appearance of signals for the proton α to the azide at δ 5.36. The reaction is quenched by the addition of 200 mL of saturated aq sodium bicarbonate. The resulting mixture is extracted three times with dichloromethane (3 x 100 mL), washed with water (3 x 100 mL), 6 N HCl (1 x 100 mL), water (1 x 100 mL), 0.1 N sodium bicarbonate (1x100 mL) and brine (1 x 100 mL). The organic extracts are dried (anhd. sodium sulfate), filtered and evaporated in vacuo. The resulting α-azido carboximide was purified by silica gel chromatography (elution with 90% hexane and 10 % ethylacetate) to give 25 g (85%) of a colorless solid. mp 84-86°C. $[\alpha]^{23}_D$ = - 25° (c 1.0, $CHCl_3$). CIMS (Isobutane), m/z (relative intensity) M^+ +1 = 365 (2%), M^+ +1-N_2 = 337 (8%), M^+ +1-HN_3 = 322 (15 %). IR ($CHCl_3$): 2103, 1771, 1698 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 1.49 (d, J=7Hz, 3H, β-CH_3), 1.98 (dd, J=13.5 Hz, 1H), 2.76-2.78 (m, 1H), 3.40-3.47 (m, 1H), 3.99 (dd, J=3.1, 9.2 Hz, 1H), 4.11 (t, J=8Hz, 1H), 4.5-4.7 (m, 1H), 5.36 (d, J=9.1 Hz, a-H, 1H), 6.96-7.0 (m, 2H), 7.22-7.36 (m, 8H). Anal. Calcd for $C_{20}H_{20}N_4O_3$ (364.39): C, 65.92; H, 5.58; N, 15.37. Found: C, 66.13; H, 5.48; N, 15.04.

(4S)-3-(2'R, 3'R)-2'-Azido-3'-(phenylbutanoyl)-4-phenylmethyl)-2-oxazolidinone, 4a. A solution of 19 g (0.059 moles) of the N-acyloxazolidinone **3a** in 145 mL of freshly distilled dichloromethane was cooled to -78°C, and then, 12.3 mL (0.07 moles) of freshly distilled diisopropylethyl amine followed by a solution of 71 mL (0.07 moles) of di-n-butylborontriflate (1M solution in DCM), was added via a cannula. The mixture was stirred for 1 hr at 0°C and cooled back to -78°C. Meanwhile, in another flask, a suspension of 12.5 g of N-bromosuccinimide (0.07 moles) in 150 mL of dichloromethane was cooled to -78°C. The boron enolate solution at -78°C was transferred via a cannula. The mixture was stirred at -78°C for 2 hr. It was then worked up according to the general procedure given above. The crude bromide was used in the next step without any purification.

From the ^1H NMR of this crude material, the ratio of major and minor isomers of the two diastereomeric bromides was found to be 99:1 (by integration of the two doublets corresponding to the diastereomeric bromides at δ 6.2). The crude bromide from the above reaction was dissolved in 100 mL of dichloromethane (or acetonitrile). Tetramethylguanidinuium azide[16a] (51 g, 0.32 moles, 5.5 eq) was added in one portion at 0°C. The mixture was warmed to and stirred at ambient temperature for 16 hr. Work-up and purification according to general procedure as above gave 18.6 g (87%) of desired azide as light yellow oil. R_f = 0.5 (8:2 hexane: ethylacetate). $[\alpha]^{23}_D$ = + 23° (c 1.0, $CHCl_3$). CIMS (Isobutane), m/z (relative intensity) M^+ +1 = 365 (2%), M^+ +1-N_2 = 337 (8%), M^+ +1-HN_3 = 322 (15 %). IR ($CHCl_3$): 2103, 1771, 1698 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ 1.49 (d, J= 7Hz, 3H, β-CH_3), 1.98 (dd, J=13.5 Hz, 1H), 2.76-2.78 (m, 1H), 3.40-3.47(m, 1H), 3.99 (dd, J=3.1, 9.2 Hz), 4.11 (t, J= 8Hz), 4.5-4.7 (m, 1H), 5.36 (d, J= 9.1 Hz, α-H), 6.96-7.00 (m, 2H), 7.22-7.36 (m, 8H); Anal. Calcd for $C_{20}H_{20}N_4O_3$ (364.39): C, 65.92; H, 5.58; N, 15.37. Found: C, 66.12; H, 5.40; N, 15.10.

(4R)-3-(2'S, 3'R)-2'-Azido-3'-(phenylbutanoyl)-4-phenylmethyl)-2-oxazolidinone, 4c. A solution of 19 g (0.059 moles) of the N-acyloxazolidinone **3c** in 145 mL of dichloromethane were cooled to -78°C

and 12.3 mL (0. 07 moles) of freshly distilled diisopropylethyl amine, followed by a solution of 71 mL (0.07 moles) of di-n-butylborontriflate (1 M solution in DCM), were transferred via a cannula. The mixture was stirred for 1 hr at 0°C and cooled back to -78°C. Meanwhile in another flask, a suspension of 12.5 g of N-bromosuccinimide (0.07 moles) in 250 mL of dichloromethane was cooled to -78°C. The boron enolate solution was transferred via a cannula. The mixture was stirred at -78°C for 2 hr. It was then worked up according to the general procedure given above. The crude bromide was used up in the next step without any purification. From the ^{1}H NMR of this crude material, the ratio of major and minor isomers of the two diastereomeric bromides was found to be 94:6 (by integration of the two doublets corresponding to the diastereomeric bromides at δ 6.2).

A small amount of this bromide (Scheme 4) was purified by silica gel chromatography (elution with 90% hexane and 10 % ethylacetate). From the eluants analytically pure bromide crystallized on standing. The bromide has the following physical characteristics: mp 94-95°C. $[\alpha]^{23}_D$ = - 38° (c 1.1, $CHCl_3$). CIMS (Ammonia), m/z (relative intensity) $M^+ + NH_3$ = 419 (40%). Anal. Calcd for $C_{20}H_{20}N\,Br\,O_3$ (402.3): C, 59.71; H, 5.01; N, 3.48; Br, 19.86. Found: C, 59.15; H, 5.00; N, 3.32; Br, 19.55.

The crude bromide from the above reaction was dissolved in 100 mL of dichloromethane (or acetonitrile) and 51 g (0.32 moles, 5.5 eq) of tetramethylguanidinium azide **16a** were added in one portion at 0°C. The mixture was warmed to and stirred at ambient temperature for 16 hr. Work-up and purification according to general procedure as above gave 17.9 g (84%) of azide **4c** as a colorless solid. mp 84-86°C. $[\alpha]^{23}_D$ = + 80.8° (c 1.0, $CHCl_3$). CIMS (Isobutane), m/z (relative intensity) M^+ +1 = 365 (2%), M^+ +1 - N_2 = 337 (8%), M^+ +1-HN_3 = 322 (15 %); IR ($CHCl_3$): 2103, 1771, 1698 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). Anal. Calcd for $C_{20}H_{20}N_4O_3$ (364.39): C, 65.92; H, 5.58; N, 15.37. Found: C, 66.13; H, 5.48; N, 15.04.

(4S)-3-(2'R, 3'S)-2'-Azido-(phenylbutanoyl)-4-phenylmethyl)-2-oxazolidinone, 4b. A solution of 30 g (0.09 moles) of the N-acyloxazolidinone **3b** in 225 mL of dichloromethane was cooled to -78°C, and 19.3 mL (1.2 moles) of freshly distilled diisopropylethylamine followed by a solution of 111 mL (1.2 moles) of di-n-butylborontriflate (1M solution in DCM), were transferred via a cannula. The mixture was stirred for 1 hr at 0°C and cooled back to -78°C. Meanwhile in another flask, a suspension of 19.7 g of N-bromosuccinimide (1.2 moles) in 225 mL of dichloromethane were cooled to -78°C. The boron enolate solution was transferred via a cannula. The mixture was stirred at -78°C for 2 hr. It was then worked up according to the general procedure given above. The crude bromide was used up in the next step without any purification. From the ^{1}H NMR of this crude material, the ratio of major and minor isomers of the two diastereomeric bromides was found to be 94:6 (by integration of the two doublets corresponding to the diastereomeric bromides at δ 6.2).

The crude bromide from the above reaction was dissolved in 150 mL of dichloromethane (or acetonitrile) and 78 g (0.49 moles, 5.4 eq) of tetramethylguanidinium azide[16a] were added in one portion at 0°C. The stirred mixture was warmed to ambient temperature for 16 hr. Work-up and purification according to the general procedure as above gave 17 g of colorless solid together with 13 g of light yellow oil. Total yield = 30 g (89%). Both the solid (mp, 84-86°C) and the oil have the same optical rotation and ^{1}H NMR. $[\alpha]^{23}_D$ = - 73°(c 1.0, $CHCl_3$). CIMS(Isobutane), m/z (relative intensity) M^+ +1 = 365 (2%), M^+ +1-N_2 = 337 (8%), M^+ +1-HN_3 = 322 (15 %). IR ($CHCl_3$): 2103, 1771, 1698cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.32(d, J=7Hz, 3H, β-CH_3), 2.58 (dd, J= 14.9, 9.4 Hz, 1H), 3.1-3.2(m, 2H), 4.1 (m, 2H), 4.6 (m, 1H), 5.23 (d, J= 9.2 Hz, 1H), 7.1-7.3 (m, 10H). Anal. Calcd for $C_{20}H_{20}N_4O_3$ (364.39): C, 65.92; H, 5.58; N,15.37. Found: C: 65.06, H: 5.32, N: 15.02.

General Procedure for the Removal of Chiral Auxiliary: Illustrated by the Preparation of (2S)-Azido-(3S)-Phenylbutanoic acid, 5d. A solution of 22 g (0.06 moles) of acylazide **4d** in 850 mL of THF and 450 mL of water was cooled to O°C and treated with 23 mL (0.24 moles) of 31% hydrogen peroxide, followed by 5 g of lithium hydroxide monohydrate (0.12 moles). The mixture was stirred for a total of 30 min. At this time, thin layer chromatography (8: 1.9: 0.1, hexane:ethylacetate:acetic acid) indicated complete disappearance of the starting material. The reaction was quenched with a solution of 30 g of $Na_2S_2O_3$ in 177 mL of water followed by a 520 mL of a solution of 0.5 N sodium bicarbonate. Tetrahydrofuran was removed *in vacuo*. Extraction with dichloromethane (5 X 100 mL) gave the recovered chiral auxiliary. The aqueous layer was cooled to 0°C and acidified with 6 N hydrochloric acid. Extraction with ethylacetate (5 x 200 mL), followed by drying (anhd. sodium sulfate), filtration and removal of solvent left the azido acid as an oil. Purification by silica gel chromatography (elution with 7: 2.9: 0.1 of hexane: ethyl acetate: acetic acid) gave 11.1 g (90%) of the title compound **5d** as a yellow oil. $[\alpha]^{23}_D$ = - 71°C 1.0, $CHCl_3$). TLC R_f = 0.57 (7 : 2.9 : 0.1, hexane : ethyl acetate : acetic acid). CIMS (Isobutane), m/z (relative intensity) M^+ +1 = 206 (38%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.38 (d, J= 7.2 Hz, 3H, β-CH_3); 3.29-3.35 (m, 1H, β-H); 4.0 (d, J= 7 Hz, 1H, α-H); 7.24-7.35 (m, 5H, aryl-H), 11.81 (S, 1H, COOH). IR (film): 2600-3400 cm^{-1} (br, OH), 2113 cm-1 (s, N_3), 1712 cm^{-1} (S, C=O). Anal. Calcd for $C_{10}H_{11}N_3O_2$ (205.1): C, 58.53; H, 5.40. Found: C, 58.54; H, 5.79.

Preparation of (2R)-Azido-(3R)-Phenylbutanoic acid, 5a. A solution of 17 g (0.046 moles) of acylazide **4a** in 650 mL of THF and 350 mL of water was cooled to O°C and treated with 17.6 mL (0.184 moles) of 31% hydrogen peroxide, followed by 3.9 g of lithium hydroxide monohydrate (0.092 moles). The mixture was stirred for a total of 30 min. At this time, thin layer chromatography (hexane: ethylacetate: acetic acid 8:1.9:0.1) indicated complete disappearance of the starting material. Work-up and purification according to the general procedure as above gave 7.5 g (80%) of pure azido acid **5a** as a light yellow oil. $[\alpha]^{23}_D$ = + 72°c 1.6, $CHCl_3$). TLC, R_f = 0.57 (7 : 2.9 : 0.1, hexane : ethyl acetate : acetic acid). CIMS (Isobutane), m/z (relative intensity) M^+ +1 = 206 (38%); ^{1}H NMR (CDCl3, 250 MHz) : δ 1.40 (d, J= 7.2Hz,

3H, β-CH_3); 3.27-3.33 (m, 1H, β-H); 4.0 (d, J= 7 Hz, 1H, α-H); 7.21-7.40 (m, 5H, aryl-H), 9.0 (S, 1H, COOH). IR (film): 2600-3400 cm^{-1} (br, OH), 2113 cm^{-1} (s, N_3), 1712 cm^{-1} (S, C=O). Anal. Calcd for $C_{10}H_{11}N_3O_2$ (205.1): C, 58.53; H: 5.40. Found: C, 59.05; H: 5.71.

Preparation of (2S)-Azido-(3R)-Phenylbutanoic Acid, 5c. A solution of 12 g (0.032 moles) of acylazide **4c** in 450 mL of THF and 175 mL of water was cooled to O°C and treated with 12.2 mL (0.13 moles) of 31% hydrogen peroxide, followed by 2.8 g of lithium hydroxide monohydrate (0.064 moles). The mixture was stirred for a total of 30 min. At this time thin layer chromatography (hexane: ethyl acetate: acetic acid 8:2.9:0.1) indicated complete disappearance of the starting material. Work-up and purification according to the general procedure as above gave 6 g (91%) of pure azido acid **5c** as a light yellow oil. $[\alpha]^{23}_D$ = - 11° (c 1.0; $CHCl_3$). TLC, R_f = 0.57 (7 : 2.9 : 0.1, hexane : ethyl acetate : acetic acid). CIMS (isobutane), m/z (relative intensity), M^+ +1 = 206 (38%). ^1H NMR ($CDCl_3$, 250 MHz) : δ 1.37 (d, J=7.2 Hz, 3H, β-CH_3); 3.34-3.46 (m, 1H, β-H); 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). Anal. Calcd for $C_{10}H_{11}N_3O_2$ (205.1) : C, 58.53; H, 5.40. Found : C, 58.05; H; 5.61.

Preparation of (2R)-Azido-(3S)-Phenylbutanoicacid, 5b. A solution of 17 g (0.046 moles) of acylazide **4b** in 650 mL of THF and 350 mL of water was cooled to O°C and treated with 17.6 mL (0.184 moles) of 31% hydrogen peroxide, followed by 3.9 g of lithium hydroxide monohydrate (0.092 moles). The mixture was stirred for a total of 30 min. At this time, thin layer chromatography (hexane : ethylacetate: acetic acid 8:2.9:0.1) indicated complete disappearance of the starting material. Work-up and purification according to the general procedure as above gave 7.7 g (82%) g of pure azido acid **5b** as a light yellow oil. $[\alpha]^{23}_D$ = +15° (c 1.3, $CHCl_3$). TLC, R_f = 0.57 (7 : 2.9 : 0.1, hexane : ethylacetate : acetic acid). CIMS (Isobutane), m/z (relative intensity), M^+ +1 = 206 (38%). ^1H NMR ($CDCl_3$, 250 MHz): δ 1.38 (d, J= 7.2 Hz, 3H, β-CH_3); 3.32-3.43 (m, 1H, β-H); 4.07 (d, J= 7 Hz, 1H, α-H); 7.24-7.37 (m, 5H, aryl-H), 11.81 (S, 1H, COOH). IR (film): 2600-3400 cm-1 (br, OH), 2113 cm-1(s, N_3), 1712 cm^{-1} (S, C=O). Anal. Calcd for $C_{10}H_{11}N_3O_2$ (205.1): C, 58.53; H; 5.40. Found : C, 57.91; H, 5.60.

Erythro-L-(2S,3S)-β-Methylphenylalanine, 6d. To a solution of 2.7 g of azido acid **5d** in 110 mL of glacial acetic acid was added 30 mL of water were added in a Parr hydrogenation vessel. A stream of argon was bubbled through this solution for 5 min. To this solution, 1 g of 10 % Pd/C was added. The mixture was hydrogenated at 30 psi for 24 hr, 100 mL of water were added and the catalyst was filtered off. To the filtrate was added 20 mL of 6 N hydrochloric acid were added and the solvents were removed *in vacuo*. To the residue was added 300 mL of anhd. ether. The precipitated solid was suction filtered and dried to give 2.2 g (80%) of the amino acid **6d** as its hydrochloride salt. A small amount of this amino acid was purified by ion-exchange chromatography (Amberlite, IR 120, H^+). Elution was done with 10 % ammonium hydroxide. The analytical data of the purified (2S,3S) erythro-L-β-methylphenylalanine is listed below: mp 182-184°C. $[\alpha]^{23}_D$ = -26.7° (c 1.0, H_2O), Lit[21] (-29°; c 1.0, H_2O). CIMS (Isobutane), m/z

(relative intensity) $M^+ +1$ = 180 (100%). ^1H NMR (250 MHz, D_2O, Dioxane as std at δ 3.55): δ 1.25, (d, J= 7.15 Hz, 3H, β-CH_3). 3.00-3.06 (m, 1H, β-H), 3.5 (d, J= 7.35 Hz, 1H, α-H); 7.13-7.26 (m, 5H, aryl hydrogens). HPLC analysis of the N-acetyl derivative[19] of this compound showed >99:1 ratio of erythro-L to threo-D isomer. Thin layer chromatography of this compound on a chiral TLC plate[23] showed only one enatiomer, R_f =0.70 (4:1:1 acetonitrile: methanol: water).

Erythro-D-(2R,3R)-β-Methylphenylalanine, 6a. To a solution of 2.7 g of azido acid **5a** in 110 mL of glacial acetic acid was added 30 mL of water were added in a Parr hydrogenation vessel. A stream of argon was bubbled through this solution for 5 min. 1 g of 10% Pd/C was added. The mixture was hydrogenated at 30 psi for 24 hr. 100 mL of water were added and the catalyst was filtered. To the filtrate, 20 mL of 6 N hydrochloric acid were added and the solvents were removed *in vacuo*. To the residue 300 mL of anhydrous ether were added. The precipitated solid was suction filtered and dried to give 2.2 g (80%) of the amino acid as its hydrochloride salt. A small amount of this amino acid was purified by ion-exchange chromatography (Amberlite IR 120, H^+) . Elution was done with 10 % ammonium hydroxide. The analytical data of the purified (2R,3R) erythro-D-β-methylphenylalanine is listed below: mp 182-184°C. $[\alpha]^{23}_D$ = + 21° (c 1.0, H_2O) Lit[21] (28.4°; c 1.0, H_2O). CIMS (Isobutane), m/z (relative intensity) $M^+ +1$ = 180 (100%). ^1H NMR (250 MHz, D_2O, Dioxane as std at δ 3.55): δ 1.22, (d, J= 7.15 Hz, 3H, b- CH_3); 3.10 (m, 1H, β-H), 3.60 (d, J=7.35 Hz, 1H, α-H); 7.31-7.42 (m, 5H, aryl hydrogens). Thin layer chromatography of this compound on a chiral TLC plate[23] showed mostly one enatiomer; R_f = 0.46 (4:1:1 acetonitrile: methanol: water). The minor diastereoisomer has R_f = 0.65 (4:1:1 acetonitrile: methanol: water). HPLC analysis[19] of the N-acetyl derivative of this amino acid showed 95:5 ratio of erythro and threo isomers. (HPLC on an achiral reverse phase cannot distinguish between enantiomers. It can only distinguish between diastereoisomers.) ^1H NMR also shows 95:5 ratio of erythro-D and threo-L isomers.

Threo-L-(2S,3R)-β-Methylphenylalanine, 6c. To a solution of 2.7 g of azido acid **5c** from the above reaction, in 110 mL of glacial acetic acid was added 30 mL of water in a Parr hydrogenation vessel. A stream of argon was bubbled through this solution for 5 min, and 1 g of 10 % Pd/C was added. The mixture was hydrogenated at 30 psi for 24 hr, then 100 mL of water were added and the catalyst was filtered. To the filtrate was added 20 mL of 6 N hydrochloric acid and the solvents were removed in vacuo. Then 300 mL of anhd. ether were added to the residue. The precipitated solid was suction filtered and dried to give 2.2 g (80%) of the amino acid as its hydrochloride salt. A small amount of this amino acid was purified by ion-exchange chromatography (Amberlite, IR 120, H^+). Elution was done with 10% ammonium hydroxide. The analytical data of the purified (2S,3R) threo-L-β-methylphenylalanine is listed below: mp 190-192°C. $[\alpha]^{23}_D$ = -5.3° (c 0.75, H_20), Lit[21] (-5.8°; c 1.0, H_2O). CIMS (Isobutane), m/z (relative intensity), $M^+ +1$ = 180 (100%); ^1H 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). Thin layer chromatography of this compound on a chiral TLC plate[23] showed only one enatiomer R_f =0.65 (4:1:1 acetonitrile: methanol:

water). HPLC analysis[19] of the N-acetyl derivative of this amino acid showed >99:1 ratio of threo to erythro isomers.

Threo-D-(2R,3S)-β-Methylphenylalanine, 6b. To a solution of 2.7 g of azido acid **5b** in 110 mL of glacial acetic acid were added 30 mL of water in a Parr hydrogenation vessel. A stream of argon was bubbled through this solution for 5 min. To this solution, 1 g of 10 % Pd/C was added. The mixture was hydrogenated at 30 psi for 24 hr. 100 mL of water were added and the catalyst was filtered. To the filtrate, 20 mL of 6 N hydrochloric acid were added and the solvents were removed in vacuo. To the residue 300 mL of anhydrous ether were added. The precipitated solid was suction filtered and dried to give 2.2 g (80%) of the amino acid as its hydrochloride salt. A small amount of this amino acid was purified by ion-exchange chromatography (Amberlite, IR 120, H^+). Elution was done with 10% ammonium hydroxide. The analytical data of the purified (2R,3S) threo-D-β-methylphenylalanine is listed below. mp 190-192°C; $[\alpha]^{23}_D$ = + 5.1 ° (c 1.1, H_2O) Lit[21] (+ 7.3°; 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 1.19 (d, J= 7.15 Hz, 3H, β-CH_3), 3.34 (m, 1H, β-H); 3.73 (d, J= 7.35 Hz, 1H, α-H) 7.16-7.27 (m, 5H, aryl hydrogens). Thin layer chromatography of this compound on a chiral TLC plate[22] showed only one enatiomer; R_f =0.54 (4:1:1 acetonitrile: methanol: water); HPLC analysis[17] of the N-acetyl derivative of this amino acid showed >99:1 ratio of threo and erythro isomers.

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